

Improving Outcomes in Patients with Kidney Disease

a practical application of evidence based medicine

Thesis submitted in fulfilment of
the requirements for the degree of
Doctor in Medicine and Health Sciences
2015

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Faculty of Medicine and Health Sciences
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To my mother

I can only hear when I truly listen

Promotors

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List of abbreviations

A

ACTH	Adrenocorticotrophic Hormone
AGREE	Appraisal of Guidelines Research & Evaluation
AIDS	Acquired Immunodeficiency Syndrome
AMSTAR	Assessing the Methodological quality of Systematic Reviews
ANZICS	Australian and New Zealand Intensive Care Society
AQP-2	Aquaporin 2
ASN	American Society of Nephrology

C

CENTRAL	Cochrane Central Register of Controlled Trials
CKD	Chronic Kidney Disease
CRH	Corticotropin-Releasing Hormone

D

DARE	Database of Abstracts of Reviews of Effects
DECIDE	Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence
DMSA	Dimercaptosuccinic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – IV

E

EBM	Evidence Based Medicine
eGFR	estimated Glomerular Filtration Rate
EMBASE	Excerpta Medica Database
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
ERBP	European Renal Best Practice
EROS	Early Review Organising Software
ESA	Endocrine Society of Australia
ESE	European Society of Endocrinology
ESICM	European Society of Intensive Care Medicine
ESKD	End Stage Kidney Disease

G

GIN	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation

K

KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KHA-CARI	Kidney Health Australia – Caring for Australasians with Renal Impairment

M

MEDLINE	Medical Literature Analysis and Retrieval System
MESH	Medical Subject Headings
MD	Mean Difference

N

NICE	National Institute for Health and Care Excellence
NKF	National Kidney Foundation

O

OR	Odds Ratio
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P

PICOM	Patients Interventions Comparators Outcomes Methodology
-------	---

Q

QUADAS	Quality of Diagnostic Accuracy Studies
--------	--

R

RCT	Randomised Controlled Trial
RR	Relative Risk

S

SIAD	Syndrome of Inappropriate Antidiuresis
SIADH	Syndrome of Inappropriate Antidiuretic Hormone secretion
SSCM	Society of Critical Care Medicine

T

TRPV1	Transient Receptor Potential Vanilloid 1
TRPV4	Transient Receptor Potential Vanilloid 4
TURP	Transurethral Resection of the Prostate

U

UTI	Urinary Tract Infection
-----	-------------------------

V

VCUG	Voiding Cystourethrogram
VUR	Vesicoureteric Reflux

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Aims and Summary



With this thesis I wish to contribute to evidence based practice in Nephrology. Not so much by expanding the theory of evidence based medicine (EBM), but by applying currently accepted methods to various aspects of evidence synthesis and guideline development. The validity of such an approach rests on the premise that the methodology used is supported by theoretic and empiric evidence, and provides more accurate and trustworthy information than any other method. For this reason this thesis starts (Chapter 2) by outlining definition and purpose of clinical practice guidelines, and discusses some of the methods central to their development. Throughout, it was not the intention to be exhaustive or even comprehensive but rather to provide the necessary rationale and background for a better understanding of the research presented in this thesis and the limitations thereof. In Chapter 3, we apply standard Cochrane methods for assessing the benefits and harms of interventions for primary vesicoureteric reflux in children through a systematic review of randomized controlled trials. In Chapter 4, we continue by extending the criteria to include non-randomized comparative and pharmacokinetic studies in a systematic review of antidepressants for depression in stage 3–5 chronic kidney disease. The two projects served as a preface to a larger one which had as its primary aim the development a clinical practice guideline on the diagnosis and treatment of hyponatraemia. In Chapter 5, we present a systematic review of guidance documents on this topic, followed by a systematic review of randomised trials assessing the benefits and harms of interventions for chronic non-hypovolaemic hypotonic hyponatraemia in Chapter 6. The guideline itself is presented in Chapter 7. Chapter 8 summarizes the main implications for practice of the presented research and discusses some of the limitations of the methodology we used. Finally, Chapter 9 is devoted to some personal reflections on what has been an exciting journey that has brought me to new lands and has taught me a more rational way of practising medicine. I hope readers will enjoy reading this thesis as much as I have enjoyed writing it.

Introduction:
**Development of clinical practice guidelines
in the care of people with kidney disease**

Chapter 2: Contents

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Definition, purpose and effectiveness of clinical practice guidelines

Definition and purpose

The Institute of Medicine defines clinical practice guidelines – hereafter referred to as guidelines – as ‘statements that include recommendations intended to optimize patient care, which are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.’

The use of guidelines began and expanded in response to issues all healthcare systems continue to face. Increasing amounts of information were gradually overwhelming clinicians who were finding it increasingly difficult to evaluate new information in context, and provide the best possible care, supported by the latest scientific developments. Healthcare costs were continuously rising, service delivery varied among providers and at least some of this variation reflected inappropriate care (both overuse and underuse of services) with resultant impacts upon patient outcomes. Guidelines were developed in an attempt to remedy these problems by providing a quality control tool for standardising and optimizing care.

Use, expected benefits and possible harms

The ultimate aim of guidelines is to improve patient outcomes by optimizing medical decision making. Initially, guidelines were conceived primarily to help individual clinicians to digest new research, and to facilitate evidence-based management decisions. By presenting contemporary evidence summaries and treatment recommendations, guideline entities aimed to improve effective practice by encouraging treatments with proven benefit and discouraging ineffective or harmful treatments.

Guidelines also serve other purposes. Guidelines may have a general educational role, teaching patients, care-givers and the media about best healthcare practices. Knowledge of a guideline may empower the individual patient to make better informed healthcare choices, by promoting shared decision making between users and providers of healthcare. Guidelines generated for conditions with little or no research evidence may be useful in additional ways. Rather than emphasizing what we know, these guidelines may predominantly serve to highlight what we don't know, and so provide justification for new research plans, and encourage stake holders and funding agencies to support new research that will close evidence gaps. Guidelines may also be used as an implementation tool, to promote translation of research evidence into everyday clinical practice. Healthcare service providers may use guidelines as a tool for standardising care, aiming to increase efficiency with a view to reducing costs. Guidelines may be used to derive measurable clinical performance indicators which can be used in quality assurance initiatives, or form the basis of financial reimbursement schemes by rewarding the use of best evidence-based practice. Publication

of guidelines may raise public awareness of previously under-recognised health burden, and inform decisions by policy makers in allocation of healthcare resources. Finally, clinicians may turn to guidelines for medico-legal protection in case of malpractice litigation.

The potential benefits of guidelines rest on the premise that guidelines are valid and their recommendations are a credible distillation of the evidence. History has often challenged this assumption. Recommendations may simply be wrong if guideline panels do not appraise all the existing evidence, give undue weight to certain findings or if the available evidence is misleading or misinterpreted. Recommendations within guidelines may be polarised if development groups fail to convene multi-stakeholder, multi-disciplinary panels, or if panel members are biased through financial or intellectual conflicts of interest.

Valid recommendations are never applicable to every single patient. It is a common misconception that guideline developers intend them to be so. If guideline recommendations are applied injudiciously, the frequently advertised benefit of more consistent practice and reduced variation in care may come at the cost of reducing individualised care for people with special needs. If guidelines are misused by auditors, there is risk of inappropriate evaluation of clinicians who purposefully deviate from the recommendations for legitimate reasons. Reimbursement incentives and fear of legal ramifications when acting outside of recommendations may prompt physicians to adhere to recommendations even when a specific clinical situation may require a practice variation. Finally even where recommendations are applicable for the individual patient, the treatment may not represent the best use of limited healthcare resources.

Evidence of effectiveness

Guidelines are able to improve care in theory, but whether they do in practice requires evaluation. Research into the effectiveness of guidelines remains limited and their effect is often hard to separate from that of other research and initiatives in the area. Examples of guidelines that have been associated with widespread and beneficial changes in practice include the National Kidney Foundation - Kidney Disease Outcome Quality Initiative (NKF-KDOQI) guidelines on vascular access and the NKF-KDOQI update of anemia guidelines. The vascular access guideline was an important catalyst for a number of changes that have seen significant increases in the use of native arterio-venous fistulae and the anaemia update, along with clinical trial evidence from the year before, has seen significant changes in haemoglobin levels in the ensuing years. Whether this translates into improved patient outcomes – e.g. fewer infections, longer and better lives – rests entirely on the evidence that underpins the relevant guidelines.

Entities providing guidelines relevant to nephrologists

There are numerous entities producing guidelines relevant to nephrology clinical practice. These include international and national nephrology entities, international and na-

Table 2.1. Examples of entities producing clinical practice guidelines relevant to nephrology.

Acronym – Guideline body	Countries	Website
Nephrology		
CSN Committee for Clinical Practice Guidelines - Canadian Society of Nephrology	Canada	www.csnsn.ca/committees/clinical-practice-guidelines/library
UK-RA United Kingdom Renal Association	UK	www.renal.org/guidelines/
KHA-CARI Kidney Health Australia – Caring for Australasians with Renal Impairment	Australia – New Zealand	www.cari.org.au/
NKF-KDOQI National Kidney Foundation - Kidney Disease Outcomes Quality Initiative	USA	www.kidney.org/professionals/KDOQI/guidelines_commentaries
ERBP European Renal Best Practice	Europe	www.european-renal-best-practice.org/
SLANH Latin-American Society of Nephrology and Hypertension	Latin America	www.slanh.org/
KDIGO Kidney Diseases Improving Global Outcomes	Global	www.kdigo.org/
ISPD International society for peritoneal dialysis	Global	www.ispd.org/ispd-guidelines/
Diabetes		
CDA Canadian Diabetes Association	Canada	www.guidelines.diabetes.ca/
ADA American Diabetes Association	USA	www.professional.diabetes.org/ResourcesForProfessionals.aspx?cid=84160
AACE American Association of Clinical Endocrinologists	USA	www.aace.com/publications/algorithm
EASD European Association for the Study of Diabetes	Europe	www.easd.org/index.php?option=com_content&view=article&id=93&Itemid=508
IDF International Diabetes Federation	Global	www.idf.org/guidelines
Hypertension		
ASH American Society of Hypertension	USA	www.ash-us.org/About-Hypertension/Hypertension-Guidelines.aspx
ESH European Society of Hypertension	Europe	www.eshonline.org/guidelines/arterial-hypertension/
ISH International Society of Hypertension	Global	www.ish-world.com/activities/guidelines.htm
General		
NICE National Institute for Health and Care Excellence	England	www.nice.org.uk/guidancemenu/conditions-and-diseases/kidney-conditions
SIGN Scottish Intercollegiate Guidelines Network	Scotland	www.sign.ac.uk/guidelines/index.html
WHO World Health Organisation	Global	www.who.int/publications/guidelines/en/
Guideline Databases		
GIN Guidelines International Network	Global	www.g-i-n.net/
NGC National Guideline Clearinghouse	USA	www.guideline.gov/
NHMRC Guidelines portal National Health and Medical Research Council	Australia	https://www.clinicalguidelines.gov.au/

tional disease-focussed societies, and government-linked organisations. There are also several useful guideline databases, permitting users to search for guidelines by topic or entity. Some of these are listed in **Table 2.1**.

Additional readings

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3. Lenzer J. Why we can't trust clinical guidelines. *BMJ*. 2013;346:f3830. <http://www.bmj.com/bmj/346/bmj.f3830>. Accessed March 14, 2015.

Methods for developing guidelines

The expected benefits of guidelines are heavily dependent upon the quality of the development process. The next sections capture the various aspects of guideline development, including topic selection; guideline group composition and group process; systematic review, synthesis and grading of the evidence; moving from evidence to recommendations; reporting and peer review.

Additional readings

1. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical Practice Guidelines We Can Trust*. Washington DC: The National Academies Press; 2011. <http://www.ncbi.nlm.nih.gov/books/NBK209539>.
2. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med*. 2012;156(7):525-531.
3. Schunemann HJ, Wiercioch W, Etzeandía I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *Can Med Assoc J*. 2014;186(3):E123-142.
4. WHO. *WHO Handbook for Guideline Development*. Geneva: World health organization; 2015.

Topic selection

Priority setting

Developing guidelines is labour-intensive and, therefore, costly. There is no empiric

evidence to guide the choice of specific methods for prioritising topics, the major (renal) guideline development bodies take similar criteria into account:

1. Domain specificity – covering topics relevant to people with kidney diseases and their carers;
2. Importance – conditions affecting many people or with great burden of illness to an individual, families, communities or society as a whole;
3. Need – perceived necessity of a guideline, as indicated by relevant stakeholders;
4. Cost – monetary cost per person of managing the health condition;
5. Variation in practice – as a proxy for clinical uncertainty over best practice;
6. Expected benefits on health outcomes from successful implementation of the guideline - potential to improve healthcare decision making for patients and providers, to improve mismatch between actual and appropriate care, to enhance care by improving patients' quality of life, reduce avoidable morbidity, or reduce avoidable premature death;
7. Availability of evidence – clinical research suggesting management strategies can produce a difference in outcomes.

The relative importance of these criteria in topic prioritisation is unclear. Most often, decisions are made implicitly. Nephrology guideline entities that use specific criteria to prioritize guideline topics, do not provide written documentation of the information which informed the specific criteria, or how this influenced judgments on relative priority of different topics. In a review of methods for priority setting commissioned by the World Health Organisation, Oxman and colleagues suggested that:

1. Criteria for establishing priorities should be applied using a systematic and transparent process.
2. Because data to inform judgements are often lacking, unmeasured factors should also be considered – explicitly and transparently.
3. The process should include consultation with potential end users and other stakeholders, including the public, using well-constructed questions, and possibly using Delphi-like procedures.
4. Groups that include stakeholders and people with relevant types of expertise should make decisions. Group processes should ensure full participation by all members of the group.
5. The process used to select topics should be documented and open to inspection.

Updating published guidelines

As medical practice develops and advances, guidelines inevitably become outdated. Successful priority setting should reveal whether updating a previously published guideline takes preference over developing a new topic. Whether an update is needed will largely be determined by the extent to which new evidence has emerged, indicating that a change in the previously advocated practice strategies could lead to better outcomes or possibly reduce cost.

Guideline adaptation and appraisal

Adapting guidelines is a means used by some guideline entities of integrating one or more guidelines produced by other entities. This may be as an alternative to developing a guideline anew, and adaptation may reduce duplication of effort and increase efficiency of guideline entities working in the same clinical arena. Adaptation may also aid collaboration between discrete guideline entities, thereby enhancing efficiency further. Adaptation might be desirable over simple endorsement, where treatment recommendations need to change to suit jurisdiction-specific constraints in delivery of care. The ADAPTE collaboration details in their manual a systematic approach to identify, appraise, and endorse or modify recommendations to suit the local context. Every guideline is assessed for quality of development and reporting using the Appraisal of Guidelines Research & Evaluation (AGREE) II instrument. AGREE II is an internationally validated, rigorously developed tool using 23 signalling questions to evaluate the quality of six domains, and provides a means for making explicit judgments about guideline quality. The structure of AGREE II is shown in **Table 2.2**.

Additional readings

1. Oxman AD, Schunemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 2. Priority setting. *Health Res Policy Syst*. 2006;4:14-21.
2. Field MJ, ed. *Setting Priorities for Clinical Practice Guidelines*. Washington DC: National Academy of Sciences; 1995.
3. Vernooij R, Sanabria A, Sola I, Alonso-Coello P, Martinez Garcia L. Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks. *Implement Sci*. 2014;9(1):3.
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6. Brouwers M, Kho ME, Browman GP, Cluzeau F, Feder G, Fervers B, Hanna S, Makarski J on behalf of the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Can Med Assoc J*. 2010, 182 (18): E839-842.

Guideline development group composition and processes

Group composition

Guideline development is not an individual's task. A multidisciplinary team is necessary for ensuring adequate consideration of the breadth of evidence and the different values at-

Table 2.2. *Structure of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument, used for appraising the quality of Clinical Practice Guidelines.*

Domain	Questions within domain
Scope and purpose	The overall objective(s) of the guideline is (are) specifically described. The health question(s) covered by the guideline is (are) specifically described. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Stakeholder involvement	The guideline development group includes individuals from all relevant professional groups. The views and preferences of the target population (patients, public, etc.) have been sought. The target users of the guideline are clearly defined.
Rigor of development	Systematic methods were used to search for evidence. The criteria for selecting the evidence are clearly described. The strengths and limitations of the body of evidence are clearly described. The methods for formulating the recommendations are clearly described. The health benefits, side effects, and risks have been considered in formulating the recommendations. There is an explicit link between the recommendations and the supporting evidence. The guideline has been externally reviewed by experts prior to its publication. A procedure for updating the guideline is provided.
Clarity of presentation	The recommendations are specific and unambiguous. The different options for management of the condition or health issue are clearly presented. Key recommendations are easily identifiable.
Applicability	The guideline describes facilitators and barriers to its application. The guideline provides advice and/or tools on how the recommendations can be put into practice. The potential resource implications of applying the recommendation have been considered. The guideline presents monitoring and/or auditing criteria.
Editorial independence	The views of the funding body have not influenced the content of the guideline. Competing interests of guideline development group members have been recorded and addressed.

Adapted and abbreviated from <http://www.agreetrust.org/> , accessed 30th March 2015

tached to possible outcomes, as well as for securing ownership and support among target audiences. Teams ideally represent the clinicians taking care of patients (e.g. nephrologists, but also other specialty disciplines, primary care physicians, nurses and paramedical staff), and other stakeholders potentially affected by implementation of the guideline (policy makers making decisions about resource use, patients and their care-givers). Guideline groups ideally also include people with expertise in epidemiology and statistics, guideline development or implementation. However, the desire for wide representation needs to be balanced against timelines and costs for bringing groups together and the challenges of effectively managing groups beyond 15 participants.

Conflict of interest

Guidelines should be based on scientific evidence, critical appraisal of the potential biases of that evidence, and objective clinical judgment in linking the evidence to what patients value. Financial or other ties to companies that are impacted by a guideline, may negatively influence the panellist's ability to approach a scientific question with an open mind. Conflict of interest may bias the interpretation of evidence, but also determine what questions

a guideline seeks to answer and unduly influence the recommendation generating process. An example that became the source of heated debate is the 2006 KDOQI guideline for the management of anaemia in people with chronic kidney disease. One recommendation therein proposed to increase the previously supported haemoglobin target concentrations from 11-12 to 11-13 g/dL, even though the available evidence indicated such an approach was not associated with better survival or reduced risk of cardiovascular events. At the time, 14 of the 16 guideline development team members reported having received consultant fees or research funds from at least one of the companies, which would potentially benefit from the guideline change. In addition, both the chair and co-chair had financial relationships with the company that funded the guideline and stood to benefit from its recommendations.

Much less acknowledged, and possibly far more difficult to deal with is intellectual conflict of interest. We often believe science to be a dispassionate pursuit of facts, and that researchers willingly change their minds as new evidence emerges. In reality, human beings often find it extraordinarily difficult to look at their own results through the eyes of a detached observer or to change their prevailing beliefs. For most entities developing renal guidelines, public disclosure of financial interests has become commonplace, but intellectual interests are rarely considered and declared intellectual conflicts rarely limit the extent to which people are permitted to participate in the guideline development process. Many experts are sceptical that disclosure alone minimizes the bias. In its standards for developing trustworthy guidelines, the Institute of Medicine has advocated exclusion of those with conflict of interest from leadership positions. The World Health Organization has adopted increasingly rigorous management strategies, excluding altogether those with conflict of interest from the recommendation generating process. Ideally, a guideline development panel would only include individuals free from conflict of interest, be it financial or intellectual. It would also include the most knowledgeable and those best able to convince others to implement the recommendations in practice. Unfortunately well-known 'experts' often have the most sweeping competing interests. Excluding them entirely from the process may not be possible without losing important insights into specific content or necessary support for effective implementation. The Institute of Medicine recognized this; rather than demanding all guideline development members be free from any competing interest, it advocated keeping their participation to a minimum.

Group processes

Although a multidisciplinary team is necessary for valid guideline development, this does not guarantee success. Successful guideline development relies on functioning group processes. What can go wrong? If one person dominates the discussion, resulting recommendations may diverge from the evidence or may not represent the opinion of the group (known as minority influence). Likewise, a desire to reach agreement may override concerns about accuracy and drive people away from the evidence (known as group think). Multidis-

disciplinary groups are especially at risk here, as established authorities are often the most active participants, and may exert undue influence over other members of lower professional status.

Group process biases may be reduced by careful selection of the group leader, who should have the authority to enforce any ground rules; ensure complete group participation by providing equal opportunities for contribution from all members; give group members' arguments proper attention when articulating recommendations; maintain constructive dynamics; and check consensus attainment while guarding their own neutrality. In the UK, the NICE guidelines entity seeks to appoint guideline working group chairs from non-topic specialties:

"The Chair is appointed for their expertise and skill in chairing groups, and although they may have some knowledge of the topic, this is not their primary role in the group. Specialist knowledge is provided by other Committee members...."

More formal group process methods include formal consensus building strategies such as nominal group techniques and Delphi methods which tend to surpass informal methods in achieving agreement. The nominal group technique is structured group brainstorming involving problem identification, solution generation, and decision making. The Delphi method is a widely used group communication process which aims to achieve a convergence of opinion from topic experts by two or more rounds of anonymous data gathering with subsequent statistical feedback.

Patient and public involvement

Quality standards increasingly stress the value of patient and public involvement in guidelines. Involving patients, their carers or advocates is necessary to ensure that their views and experiences are reflected, that the guideline is patient-centred and that it covers issues and outcomes important to them. However, best methods of adequately soliciting consumer perspectives are not clear, and take time and money. If done without proper thought to the aims and required methods for achieving integration of consumer perspectives, attempts risk remaining tokenistic, leaving consumers with a marginal role at best.

In 2012, G-I-N PUBLIC, a workgroup of the Guidelines International Network devoted to effective patient and public involvement in the development and implementation of guidelines, identified three strategies important for patient and public involvement. These were:

1. Consultation – aiming to collect views regarding needs, experiences, and expectations. This can happen at the scoping stage or when the draft guideline has been developed, be targeted to relevant consumer groups or open to the public, or both. Consultation may include inviting comment on draft documents, centre on systematic reviews of patient and public perspectives, and include surveys, focus groups or individual interviews.
2. Participation – aiming to have active involvement in deliberation, to foster a collective perspective on guideline development and to agree on common group decisions over guideline content. Although in theory, participation can facilitate compromise between

people with varying perspectives, adequate support is required for it to be effective.

3. Communication - aiming to provide patients and public with understandable information on diagnostic or treatment recommendations, enabling joint decision-making based on the best available evidence.

For nephrology guidelines groups, the engagement of patients and the broader community with their work remains limited and in need of development.

Additional readings

1. Eccles M, Grimshaw J, Shekelle P, Schunemann H, Woolf S. Developing clinical practice guidelines: target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. *Implement Sci.* 2012;7(1):60-67.
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6. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Asses.* 1998; 2 (3) :i-iv 1-88.
7. G-I-N PUBLIC toolkit: Patient and Public Involvement in Guidelines. <http://www.g-i-n.net/working-groups/gin-public/toolkit>. Accessed March 14, 2015.

Systematic literature review/Development processes

Scoping/Determining key questions and outcomes

This is possibly the most important phase of the guideline development process, but team impetus to move forwards to evidence review is sometimes at odds with spending time deliberating guideline questions and outcomes. Arriving at an evidence-based recommendation requires understanding which questions must be answered to get there, what evidence is available for consideration, and what outcomes need to be assessed. Typically, questions include identification of groups at risk of a health problem, diagnostic test accuracy, benefits and harms of different treatments, significance of prognostic factors, etc. For example, to develop a recommendation for or against screening for cardiovascular disease in kidney transplant candidates, one would need to know; if there are effective treatments to improve outcomes in candidates with severe asymptomatic coronary artery disease; if tests can accurately diagnose the condition: the potential harms of testing and treatment; and who should be screened. Failure to articulate these key questions and to define which

evidence is admissible to answer them can result in time, effort and money wasted at gathering and analysing data that is ultimately irrelevant to the recommendations being developed.

Consider an example; if you tried answering a question on 'how best to screen for cardiovascular disease in kidney transplant recipients?' How would you go about finding an answer? You could turn to an internet browser and search the question verbatim. In Google it would take 0.37 seconds to retrieve 179,000 citations (as of 6th April 2015), including guidelines and consensus statements and, if lucky, these would be at the top of the list and provide trustworthy advice. More likely is that these were buried among many other entries, more or less relevant to the topic. There may be a few systematic reviews and hundreds of individual studies investigating the incidence of cardiovascular disease among kidney transplant candidates; the risk factors associated with having asymptomatic coronary artery disease; the diagnostic accuracy of various non-invasive tests in detecting disease; the association between asymptomatic coronary disease before and the outcome after transplantation; and benefits and harms of treatments for asymptomatic disease before transplantation. Most of the retrieved studies regarding a given question will cover different patient groups. In addition, there will be thousands of citations unrelated to the problem. Finally, you may have missed crucial information not picked up by the browser's search algorithm.

The example above illustrates that efficiently generating evidence-based advice requires understanding i) which questions need to be answered in what order ii) what evidence is required and iii) how to adopt a systematic strategy that will allow its retrieval.

Guideline development team members must unambiguously define which outcomes and which measurement time-points they consider pivotal for decision making. This step forces the team to articulate in advance to what extent particular outcomes need to be affected to support a particular recommendation. Outcomes must reflect what is important to patients. In the example of screening for cardiovascular disease, it is likely that patient-centred outcomes would include all-cause and cardiovascular death as well as severe complications such as acute myocardial infarction. Important outcomes may also include indicators of physical or emotional well-being such as functional status or health-related quality of life. Data on these health-outcomes are often harder to ascertain, as clinical trial investigators tend to measure surrogate outcomes to reduce the cost, sample size and duration of trials. However, assumptions about proximity of surrogates to clinically important outcomes are often not well informed. For example, it is tempting to assume benefits of lipid-lowering treatment on total cholesterol will result in downstream reduction in cardiovascular death, but this may not be the case for people with ESKD.

Framing questions for systematic review: PICOM

Individual key questions must be framed such that relevant evidence can be systematically searched and selected. Framing is facilitated by addressing each part of the mnemonic PICOM.

- **P - Patient** and/or **Problem**. How would one define a group of patients akin to the ones of interest? What are key common characteristics of these people?
- **I – Intervention** or **Indicator**. Which main interventions should be contemplated? What diagnostic test or exposure?
- **C – Comparison**. What is the main alternative with which the intervention/indicator is to be compared? Is this about a comparison between two medications, a medication and no treatment, or two diagnostic tests?
- **O – Outcomes**. What is/are the outcome(s) of most interest in this clinical setting? Are clinicians or patients seeking benefit or reduced adverse events?
- **M – Methodology**. What is the best feasible study design to answer this question? Which study design will offer the least biased results?

Table 2.3 shows how the clinical question on screening for coronary artery disease in kidney transplant candidates can be divided in sequential specific questions and converted into a focused format more readily answerable by research evidence, by applying the above PICOM strategy.

Systematic searching and study selection

Information sources

Once the precise guideline questions have been framed into an answerable format, the next step is to determine where to best look for an answer. Medical research data are most effectively accessed through queries of electronic databases which offer citations and abstracts of journal articles and books. There is a wide variety of such databases available and the 'best' choice will largely depend on the type of question being asked and the optimal study design to answer that question. There are many databases with overlapping, complementary or unique content areas and each has its strengths and weaknesses. It is beyond the scope of this paper to cover all options. Hence, discussion will be limited here to the databases most immediately useful to guideline developers: The Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), the Medical Literature Analysis and Retrieval System (MEDLINE), and the Excerpta Medica Database (EMBASE) platform.

Table 2.4 shows the specific databases most useful to search for the clinical questions developed earlier in this paper, organised by question type and optimal study design.

Search strategy structure

Executing an effective search to identify all studies relevant to the specific question at hand is a critical and often challenging step in the guideline development process. Identifying the totality of evidence for a question must appreciate the quantity of published and unpublished material is vast; much research remains unpublished; there are limitations in indexing systems within electronic databases, and in the scope of individual databases; sensitive searching has to come at the cost of retrieving irrelevant studies, and specific searches

Table 2.3. From clinical question to framed guideline questions using PICO format.

Clinical question – What is the best way to screen kidney transplant candidates for coronary artery disease?			
Specific question	Rationale	Requirement	PICO framework
What is the incidence of cardiovascular mortality in kidney transplant candidates?	If cardiovascular mortality was non-existent, there would be no rationale for screening for it.	The condition should be an important health problem.	Background question – found in textbooks, registry reports
What is the association between severe coronary artery disease and future risk of cardiovascular mortality in kidney transplant candidates?	If there is no relation between coronary artery disease and cardiovascular death, then there would no rationale in treat it.	There should be a latent stage of the disease. The natural history of the disease should be adequately understood.	P – Kidney transplant candidates I – Coronary artery disease C – No coronary artery disease O - Death M – Diagnostic study, Systematic review
In transplant candidates, is treatment of asymptomatic coronary artery disease effective at reducing cardiovascular mortality before and after transplantation?	If there is no treatment available for which the benefits outweigh the harms, then detecting the disease may not be useful.	There should be a treatment for the condition. There should be an agreed policy on whom to treat.	P – Kidney transplant candidates with asymptomatic coronary artery disease I – Percutaneous coronary intervention, coronary artery bypass grafting, medical treatment C – No treatment O - Death M – RCT, Systematic review
In transplant candidates, what is the diagnostic test accuracy of non-invasive investigations for detecting asymptomatic coronary artery disease?	If there is no test available that can detect the disease with reasonable accuracy then there is no rationale for screening. If the test is unacceptable for patients, attempting to screen will not work.	There should be a test or examination for the condition. The test should be acceptable to the population.	P – Kidney transplant candidates I – Resting electrocardiography, exercise stress electrocardiography, dobutamine stress echocardiography, myocardial perfusion scintigraphy C – Coronary angiography O – Coronary artery disease M – Cohort study, Systematic review

RCTs: randomised controlled trials

Table 2.4. Framed questions, recommended study designs and databases to search.

Question	Study design	Database	Provider/platform	Content
What is the association between severe coronary artery disease and future risk of cardiovascular mortality in kidney transplant candidates?	Systematic review of cohort studies Cohort studies	MEDLINE EMBASE	PubMed, Ovid Elsevier, Ovid	Systematic reviews, RCTs, cohort studies, case-control studies, case reports, diagnostic cross-sectional studies, editorials...
In transplant candidates, is treatment of asymptomatic coronary artery disease effective at reducing cardiovascular mortality before and after transplantation?	Systematic review of RCTs RCTs	CDSR DARE CENTRAL MEDLINE EMBASE	The Cochrane Library, Ovid The Cochrane Library, Ovid The Cochrane Library, Ovid PubMed, Ovid Elsevier, Ovid	Cochrane systematic reviews of RCTs Non-Cochrane systematic reviews of RCTs RCTs Systematic reviews, RCTs, cohort studies, case-control studies, case reports, diagnostic cross-sectional studies, editorials...
In transplant candidates, what is the diagnostic test accuracy of non-invasive investigations for detecting asymptomatic coronary artery disease?	Systematic review of cross-sectional diagnostic studies Cross-sectional diagnostic studies	MEDLINE EMBASE MEDLINE EMBASE	PubMed, Ovid Elsevier, Ovid PubMed, Ovid Elsevier, Ovid	Systematic reviews, RCTs, cohort studies, case-control studies, case reports, diagnostic cross-sectional studies, editorials... Systematic reviews, RCTs, cohort studies, case-control studies, case reports, diagnostic cross-sectional studies, editorials...

may miss important evidence and individuals who are experts in the content area may believe they already know all the relevant research within a particular field.

A typical search strategy consists of a logical combination of terms referring to the population; the intervention, index test or exposure; possibly the comparator; the outcomes; and finally the study design. For each of the components, relevant search terms include a combination of keywords database providers use to index the publications and documents listed within their database. These keywords make up the controlled vocabulary thesaurus (e.g. MeSH for MEDLINE and the Cochrane Library; Emtree for EMBASE) and allow simultaneous retrieval of similar articles without specifying each synonym and spelling variation used by authors. Because indexing is at times subjective and incomplete, systematic search strategies typically include free text words (in title and abstract) to ensure important citations are not missed. **Table 2.5** shows an example of a framed question translated into a sensitive search strategy.

Systematic evidence review including bias appraisal of included studies

What is bias and why should it be considered?

A bias is a systematic error or deviation from the truth, in results or inferences which can lead to either over- or underestimation of the causal relationship between an intervention, an exposure or a diagnostic test, and an outcome. Bias results from factors which may be known or unknown, which provide a possible alternative explanation for the result attributed to the relationship between the intervention of interest and the outcome. Such factors have three features: i) they affect the outcome, e.g. age; ii) they are unequally distributed between the experimental and control group; iii) they do not represent an intermediate step in the causal chain between the exposure and outcome. In practice it is impossible to know to what extent biases affect the results of any individual study, but there is substantial evidence that specific shortcomings in the design, conduct or analysis of studies result in bias. Some study designs are inherently more vulnerable to the introduction of bias than others. For example, the RCT differs from an observational cohort study in that the randomization aims to protect against selection bias whilst the blinding of participants and personnel tries to minimise performance bias. However, not all RCTs produce equally trustworthy results, as not all are conducted and reported optimally. RCTs produce treatment effect estimates that are; exaggerated by 11% if the sequence generation is inadequate or unclear; exaggerated by 7% if the allocation concealment is inadequate or unclear; and exaggerated by 13% if blinding of participants and researchers does not occur. Estimates of exaggeration are greatest for meta-analyses assessing subjective outcome measures.

Because each type of study (e.g. RCT versus cohort study) has different opportunities for introducing bias, any assessment tool aiming to distinguish studies providing more or less trustworthy results, needs to be tailored to the particular study design under evaluation.

Table 2.5. *Anatomy of search strategy - In transplant candidates, is treatment of asymptomatic coronary artery disease effective at reducing cardiovascular mortality before and after transplantation?*

P	Kidney transplant candidates	<p>#1 MeSH descriptor: [Kidney Transplantation] this term only #2 (kidney or renal) next transplant*:ti,ab,kw #3 #1 OR #2</p> <p>#1 Controlled vocabulary term to index articles about kidney transplantation, will include articles in which authors use 'renal transplantation', 'renal grafting', etc. #2 Addition of text words 'kidney transplantation' and 'renal transplantation' as a safety net to pick up articles that were indexed incompletely or incorrectly. 'Next' used as Boolean operator to indicate the words kidney or renal need to be adjacent to 'transplantation' in title, abstract or listed keywords. #3 Boolean operator 'OR' indicating inclusion of all citations indexed as kidney transplantation plus all citations picked up by line #2, including all with both.</p> <p>#4 MeSH descriptor: [Cardiovascular Diseases] this term only #5 MeSH descriptor: [Myocardial Ischemia] explode all trees #6 coronar*:ti,ab,kw #7 #4 OR #5 OR #6 #8 #3 AND #7</p> <p>#5 Controlled vocabulary term to index articles about myocardial ischemia. 'Explode all trees' is an option allowing inclusion of all terms hierarchically positioned underneath 'Myocardial Ischemia', e.g. 'Angina Pectoris' and 'Coronary Diseases'. #8 Boolean operator 'AND' indicating inclusion of all citations picked up by line 3 and line 7 at the same time, the cross section of both searches.</p>	<p>#10 * is a truncation symbol, retrieves any number of characters after the word stem or no characters.</p>
I	Percutaneous coronary intervention	<p>#9 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees #10 PCI*:ti,ab,kw #11 #9 OR #10</p> <p>#12 MeSH descriptor: [Coronary Artery Bypass] explode all trees #13 CABG*:ti,ab,kw #14 #12 or #13</p>	
C	Coronary artery bypass grafting		
C	Medical treatment	-	If the comparator is no specific treatment or standard care, which would also be given to the 'interventional' group, then this is usually not included in the strategy to allow adequate sensitivity.
O	Death	-	For questions concerning interventions, outcome terms are usually not included to allow adequate sensitivity.
M	Systematic review of RCTs	<p>1 Review.pt AND Medline.tw. 2 Meta analysis.pt 3 (systematic* AND (review* OR overview*)) :tw 4 metaanaly*:tw 5 meta-analy*:tw 6 OR/1-5</p>	<p>In The Cochrane Library, both CDSR, DARE and CENTRAL are searched simultaneously. Because CDSR and DARE preferentially include systematic reviews, methodological filters are not required. The syntax provided here is intended for MEDLINE via OVIDSP. Searches for MEDLINE via PubMed are similar in structure, details of the syntax may differ somewhat. For details see (National Library of Medicine-Library).</p> <p>Because CENTRAL preferentially includes RCTs, methodological filters are not required when searching the Cochrane Library. 1 'pt' – publication type. Articles indexed as being a randomized controlled trial are searched. 3 articles with the word 'randomized' in the abstract are searched. 7 articles with the word 'randomly' in the title are searched. 10 The Boolean operator 'NOT' indicates articles selected in line 9 are excluded. Lines 9 and 10 together exclude studies exclusively conducted in animals.</p>
	RCTs	<p>1 randomized controlled trial.pt 2 controlled clinical trial.pt 3 randomized.ab 4 placebo.ab 5 clinical trials as topic/ 6 randomly.ab 7 trial:ti 8 OR/1-7 9 animals/ NOT (humans/ AND animals/) 10 8 NOT 9</p>	

Tools for assessing risk of bias in studies

Risk of bias can be used interchangeably with internal validity or the extent to which design and conduct of a study are likely to have prevented biases. Many tools have been developed to aid the assessment of potential bias in studies of different designs, each with their own strengths and weaknesses. **Table 2.6** lists a suggested bias assessment tool for each study design. Without exception these tools are the result of consensus between statisticians, epidemiologists and review authors, based on systematic review of empirical evidence.

Appraising a body of evidence for individual outcomes across studies

Regardless of the primary aim of the guideline literature review (comparing interventions, assessing the accuracy of a test or estimating the average effect of a risk factor), the next step is to examine the totality of evidence for each outcome across studies and draw conclusions about the summary effect. The degree of confidence in these conclusions will depend on several factors. The reliability of results of the individual studies is not the only determinant. Other features include evaluating the consistency and precision of the results across studies, applicability of results to the targeted population and whether publication bias is likely.

Consistency of evidence relates to heterogeneity of findings across studies. Study results can vary due to differences in key aspects of the design (e.g. trials with lower or higher risk of bias) or of the study participants (e.g. those treated versus those not yet treated with dialysis), interventions (e.g. doses, duration of treatment, co-interventions) and outcomes (e.g. definitions and measurement time-point). If important variability among studies remains unexplained, it will reduce the confidence in any resulting inferences. Assessing the importance of a level of variability remains a matter of judgement of the assessors.

Directness of evidence is also referred to as applicability or external validity. Examples of features that can reduce the applicability of evidence to a guideline include differences between the study participants and the population for which the guideline is meant to apply. This might be driven by difference in baseline risk, in culture, lifestyle, delivery of care, or in the availability of technologies and resources. Directness is also compromised if measured study outcomes differ from those the guideline development team see as critically important (e.g. Kt/V versus health-related Quality of Life); or if surrogate outcomes are used instead of important patient outcomes (e.g. 30% decrease in glomerular filtration rate versus need for renal replacement therapy).

Precision relates to confidence in the magnitude of an estimated effect. Precision is usually represented by the 95% confidence interval, which can be interpreted as the range within which the effect plausibly lies. The confidence interval needs to be sufficiently narrow, and to encompass the minimal effect considered clinically important.

Publication bias occurs if 'negative studies' remain unpublished or unidentified. When only published studies are considered, interventions appear more effective, tests more ac-

Table 2.6. *Tools for assessing risk of bias/Critical appraisal tools.*

Study design	Tool	Bias	Mechanism
Ran- domised controlled trials	Cochrane risk of bias tool for randomised controlled trials	Selection bias Selection bias Performance bias Detection bias Attrition bias Reporting bias Other bias	1 Bias due to inadequate random sequence generation 2 Bias due to inadequate allocation concealment 3 Bias due to inadequate blinding of participants and researchers 4 Bias due to inadequate blinding of outcome assessment? 5 Bias due to incomplete outcome data 6 Bias due to selective reporting 7 Bias due to other mechanisms
Non-ran- domised studies of interven- tions	A Cochrane risk of bias assessment tool: for non-ran- domized studies of interventions (ACROBAT – NRSI)	Confounding bias Selection bias Misclassification bias Performance bias Attrition bias Detection bias Reporting bias	1 Bias due to confounding 2 Bias in selection of participants into the study 3 Bias in measurement of interventions 4 Bias due to departures from intended interventions 5 Bias due to missing data 6 Bias in measurement of outcomes 7 Bias in selection of the reported result
Cohort studies	Newcastle-Ottawa quality assessment scale cohort studies (NOS – Cohort)	Selection bias Selection bias Misclassification bias Detection bias Selection bias Detection bias Detection bias Attrition bias	1 Representativeness of exposed cohort 2 Selection of the non-exposed cohort 3 Ascertainment of exposure 4 Demonstration that outcome was not present at start of study 5 Comparability of cohorts on basis of the design and analysis 6 Assessment of outcome 7 Adequacy length of follow-up for outcome occurrence 8 Adequacy of follow-up of cohorts
Case- control studies	Newcastle-Ottawa quality assessment scale cohort studies (NOS – Case-control)	Selection bias Selection bias Selection bias Selection bias Selection bias Detection bias Detection bias Attrition bias	1 Adequacy of case definition 2 Representativeness of cases 3 Selection of controls 4 Definition of controls 5 Comparability of cases and controls on the basis of the design or analysis 6 Ascertainment of exposure 7 Same method of ascertainment for cases and controls 8 Non-response rate
Cross- sectional diagnos- tic test accuracy studies	Quality assess- ment of studies of diagnostic accuracy (QUADAS-II)	Selection bias Spectrum bias Performance bias Detection Bias Performance bias Performance Bias Attrition bias	1 Bias in selection of participants into the study 2 Applicability of test results to target population of interest 3 Bias in conduct or interpretation of the index test (blinding) 4 Applicability of index test, its conduct, or interpretation to review question 5 Bias in conduct or interpretation of reference standard 6 Applicability of target condition as defined by reference standard to review question 7 Bias through patient flow
Systematic review	Assessing the meth- odological quality of systematic reviews (AMSTAR)	Reporting bias Selection bias Selection bias Publication bias Publication bias Selection bias Information bias Information bias Detection bias Publication bias Conflict of interest bias	1 Was an 'a priori' design provided? 2 Was there duplicate study selection and data extraction? 3 Was a comprehensive literature search performed? 4 Was the status of publication (i.e. grey literature) used as an inclusion criterion? 5 Was a list of studies (included and excluded) provided? 6 Were the characteristics of the included studies provided? 7 Was the scientific quality of the included studies assessed and documented? 8 Was the scientific quality of the included studies used appropri- ately in formulating conclusions? 9 Were the methods used to combine the findings of studies ap- propriate? 10 Was the likelihood of publication bias assessed? 11 Was the conflict of interest included?

curate and risk factors more important. It is difficult to formally assess for publication bias outside of the systematic review setting, and statistical methods for estimating the magnitude of the problem all have their limitations.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, provides a framework to facilitate formal evaluation of the reliability of a body of evidence (**Table 2.7**).

Additional readings

1. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology* 2011;64(4):395-400.
2. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
3. Sterne JAC, Higgins JPT, Reeves BC, et al. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT- NRSI), Version 1.0.0. <http://www.riskofbias.info>. Accessed March 14, 2015.
4. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med*. 2012;157(6):429-38.
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7. Shea B, Grimshaw J, Wells G, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7(1):10-16.
8. Scottish Intercollegiate Guidelines Network (SIGN). Chapter 5: Assessing the quality of evidence. In: SIGN 50: a guideline developer's handbook. Edinburgh, Scotland. SIGN; 2014:89-106. <http://www.sign.ac.uk>.
9. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines 3: rating the quality of evidence - introduction. *J Clin Epidemiol*. 2011;64(4):401-406.
10. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *Journal of clinical epidemiology*. 2011;64(4):380-382.

Generating recommendations

Rating strength of recommendations and quality of the evidence across key outcomes

A recommendation is an individual statement proposing the best course of action for a given situation. It can be for or against a strategy with varying degrees of conviction. The

Table 2.7. GRADE method of rating the quality of the evidence.

Step 1: Starting grade according to study design	Step 2: Lower if	Step 3: Higher if	Step 4: determine final grade for quality of evidence
Randomized trials = High	Risk of Bias -1 Serious -2 Very Serious	Large effect +1 Large +2 Very Large	High (four plus: ⊕⊕⊕⊕)
Observational Studies = Low	Inconsistency -1 Serious -2 Very Serious	Dose response +1 Evidence of a gradient	Moderate (three plus: ⊕⊕⊕○)
	Indirectness -1 Serious -2 Very Serious	All plausible confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect when results show no effect	Low (two plus: ⊕⊕○○)
	Imprecision -1 Serious -2 Very Serious		Very Low (one plus: ⊕○○○)
	Publication Bias -1 Likely -2 Very likely		

GRADE specifies four categories for the quality of a body of evidence: from high to very low. The quality of evidence for an outcome is initially rated high if it originates predominantly from randomised controlled trials and low if it originates from observational data. These ratings can be subsequently downgraded or upgraded if any of a number of additional criteria are met Adapted from Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence.

J Clin Epidemiol. 2011;64(4):401–406.

strength of a recommendation is determined by the quality of the evidence across key outcomes, but also by judgments related to the balance between the desirable and undesirable effects of a strategy, the variability in values and preferences and the associated costs. Clear communication of both the intended message and the value judgements that influence the recommendation generating process is key.

Guideline developers apply formal approaches for separately rating the strength of recommendations and the overall quality of the underlying evidence, resulting in the assignment of categorical scores. The GRADE system is currently the most widely used and has been adopted by all major renal guidelines organisations. It categorizes recommendations as 'strong' if benefits or harms clearly outweigh one another, the confidence in the evidence for important health outcomes is high, healthcare consumers agree on the value of different outcomes and the proposed strategy represents a wise use of resources. It categorizes recommendations as 'weak' if the trade-offs between benefits and harms are less certain, because of low quality evidence, because high quality evidence suggests that wanted and

unwanted effects are closely balanced, because healthcare consumers have diverging ideas on which outcomes matter most to them, or because the proposed strategy may be very costly. Although, the discrete approach to rating recommendations can be criticised for categorizing what in reality is a continuum, it has the benefit not only of simplicity, but also of direct associations to actions on the part of patients and policy makers. To communicate the overall quality of the evidence supporting a recommendation, a summary rating, ranging from 'high' to 'very low' is assigned representing the lowest quality of evidence for any of the outcomes that are critical to decision making. **Figure 2.1** provides a worked example about how the GRADE approach works in practice.

Articulating recommendations

It is reasonable to assume specific wording influences how statements are interpreted and whether or not they can be implemented consistently by clinicians. Most renal guideline organizations use the specific terminology proposed by GRADE to confer the strength of a recommendation: 'we recommend' (either in favour or disfavour) for a strong statement, and 'we suggest' (either in favour or disfavour) for a weak statement. This standardisation of language and methods is a positive evolution, as it increases consistency in how recommendations are to be interpreted. Often however, recommendations have been criticized for being non-specific, failing to indicate precisely under which conditions to do what. Vague recommendations using structures such as 'patients with condition A should receive treatment B *if considered necessary*', are usually not very useful in clinical practice as they are dependent upon the interpretation of what constitutes necessity. A well worded recommendation should specify the population as well as the specific conditions under which it applies. Unless it is obvious, it should also specify the comparator. Consider for example the following statement: "In patients at increased risk of contrast-induced acute kidney injury, we recommend intravenous volume expansion with isotonic saline or sodium bicarbonate". Here, the strength of this recommendation may differ depending on whether the alternative is oral hydration or no hydration at all.

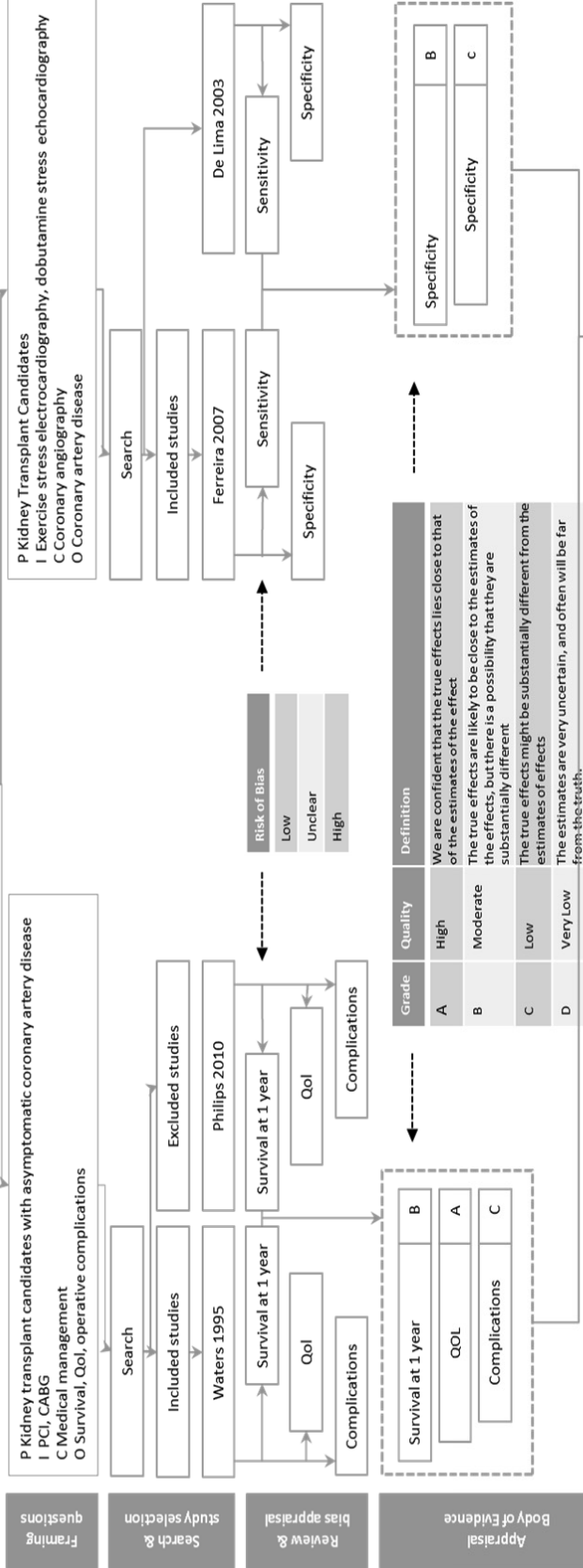
Additional readings

1. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol.* 2012;66(2):151-157.
2. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol.* 2013;66(7):726-735.

Reporting and peer review

Reporting refers to how a guideline will be made public (e.g., print, online), and the level

Whether and how to screen for coronary artery disease in potential kidney transplant recipients



Grade	Patients	Clinicians	Implications	Policy
1 - strong 'We recommend'	Most people in your situation would want the recommended course of action, only a small proportion would not	Most patients should receive the recommended course of action		The recommendation can be adopted as a policy in most situations
2 - weak 'We suggest'	Most people in your situation would want the recommended course of action, but many would not	You should recognise that different choices will be appropriate for different patients. You must help each patient to arrive at a management decision consistent with her or his values and preferences.		Policy making will require substantial debate and involvement of many stakeholders

We suggest screening potential kidney transplant recipients for significant coronary artery disease with dobutamine stress echocardiography rather than with myocardial perfusion scintigraphy. (2C)

Strenght	2
Level of Evidence	C

of detail contained within the guideline document. Peer review refers to how the guideline document will be reviewed before its publication and how the guideline can be assessed both internally, as well as externally by stakeholders who were not members of the guideline development team.

Reporting a guideline

The user casts the ultimate verdict on a guideline's trustworthiness. An informed decision requires detailed description of the methods used for developing the guideline including all items covered in the other sections (above and below) in this paper. In addition, in reporting a guideline it is essential to provide a narrative rationale describing the link between every recommendation and its supporting evidence in order for a user to judge the extent to which the recommendations can be justified. The narrative should cover both anticipated benefits and potential risks associated with implementation of the guideline recommendations. In 2003, a conference on guideline standardisation proposed a list of 18 core items to report for a guideline. The major organisations producing guidelines for patients with kidney diseases currently use similar formats, covering the majority of the expected items.

External review

A guideline development group is limited in the knowledge it can bring to the table and the perspectives it can offer. External review helps to ensure balance, comprehensiveness, accuracy of the scientific evidence, validity of the rationale for recommendations, allows feedback on the clarity and feasibility of recommendations and contributes to engagement of stakeholders. There are several types of external review, serving different purposes and requiring input from different people.

Reviewers can be specifically invited, usually for their perceived ability to contribute. They may include leading clinical researchers or key opinion leaders, asked to identify missing research, and mistakes in the description of studies, interpretation of their quality, or reporting of their results. In addition, expert peer-reviewer contribution may increase a sense of ownership and support of those who are most influential. Invited reviewers may include methodologists, specifically to identify possible biases, asymmetry in the presentation of evidence or flaws in the logic applied in translating the evidence into recommendations. Invited reviewers may also include targeted practicing clinicians, with the aim of identifying any ambiguities in the recommendations when they are used in practice or effects on work-

Figure 2.1. (opposite page) *From framing the question to generating the recommendation, a worked example of whether and how to screen for coronary artery disease in potential kidney transplant recipients.*

CABG – Coronary Artery Bypass Grafting; GRADE—Grading of Recommendations, Assessment, Development and Evaluation; PCI – Percutaneous Coronary Intervention; QOL – quality of life.

flow that may hamper implementation. Other peer reviewers may include representatives from federal agencies, professional organizations, specialty societies, healthcare providers, peer review journals, and relevant guideline panels authoring related guidelines. They may include representatives from advocacy organizations, community groups, and public health organizations whose constituents may be affected by the guideline; and representatives businesses and industries, pharmaceutical or device manufacturers impacted by the guideline.

A draft guideline may also be put up for public consultation. In this case, typically the guidelines are posted on the internet for a defined time period, and open for comment by any interested party. Public consultation provides an opportunity to create a sense of partnership, which may increase acceptability of the guideline as a whole and help in promoting awareness and adoption of the recommendations.

Finally, guideline developers can also choose to include peer review through publication in a peer-reviewed journal. This may have the advantage of obtaining scientific credibility and facilitate implementation through outreach to the readership of the journal. Disadvantages include delays due to the peer-review process, and external control over guideline release dates. A possible drawback is the potential for Editors to exert undue influence over the guideline content, insisting on changes based on comments of a few reviewers which may or may not be substantiated by the evidence and agreed methodology.

Regardless of the type of external review, methods for dealing with criticism should comply with development methodology, and criticism can never simply be ignored. Groups need to adopt a system for recording, discussing and processing elicited comments. Care needs to be taken that responses are adequately communicated, given guideline implementation resistance often comes from insufficient understanding of the methodology used.

Additional readings

1. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized Reporting of Clinical Practice Guidelines: A Proposal from the Conference on Guideline Standardization. *Ann Int Med.* 2003;139(6):493-498.
2. Shekelle P, Woolf S, Grimshaw JM, Schunemann HJ, Eccles MP. Developing clinical practice guidelines: reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues of enhancing guideline implementability and accounting for comorbid conditions in guideline development. *Implement Sci.* 2012;7:62-68.

Implementation of guidelines

Producing a guideline does not change practice. The next step is guideline implementation. Detailed exposition on implementation science is beyond the scope of this paper, but a brief overview is warranted. The aphorism that “guidelines don’t implement themselves” poses a challenge for guideline developers, as implementation requires quite a different set of skills and resourcing from those required to develop the guideline. Implementation of guidelines requires that clinicians or patients are aware of the guideline, understand the guideline and its implications for their service and patient care, and consider it important enough to invest in changing their practice to more closely reflect the guideline recommendations. Within this voyage from evidence summation to implementation there are many potential barriers at the various layers of the healthcare delivery system, such that it is not surprising that most guideline development groups concede the responsibility of implementation to health service delivery organisations.

Dissemination

The easiest part of guideline implementation is dissemination. There are numerous portals through which guidelines can be publicised, with most renal guidelines groups publishing their guidelines in peer-reviewed journals as well as on their websites (*Table 2.1*). Many guidelines groups also publicise their products using the more usual tools that researchers employ, such as in the proceedings of Scientific Meetings, as well as publicising document through local specialty societies. With the increasing availability of mobile internet devices, smartphone applications that summarise clinical guidelines are also becoming more widely used (eg: KDIGO, NICE). However, dissemination alone is not a very effective tool for driving practice change.

Additional implementation challenges

Beyond informing clinicians about the guideline, the more effective guideline implementation tools share common ground with healthcare quality improvement and assurance methods. These use methodologies including audit and feedback, barrier analyses, involvement of key opinion leaders and extend to the use of reminder systems and multifaceted interventions delivered at multiple levels of the healthcare system. The commonest approach used to address guideline–practice gaps in healthcare is the Plan-Do-Study-Act cycle, designed to be applied in iterative cycles, to generate and analyse data from a healthcare process, use results to develop interventions to alter that process and measure the effect of these interventions before developing further actions (*Figure 2.2*). However, development of new implementation methods and evaluation of existing strategies is on-going, and is likely to evolve further in coming years. Clearly these methods require quite different skill sets from the development of the guideline itself, as well as significant investment in

staff time and project infrastructure. Organisations that fund and manage health systems are likely to be best placed to drive such processes but may also be the groups least likely to be aware of the guideline evidence.

Additional readings

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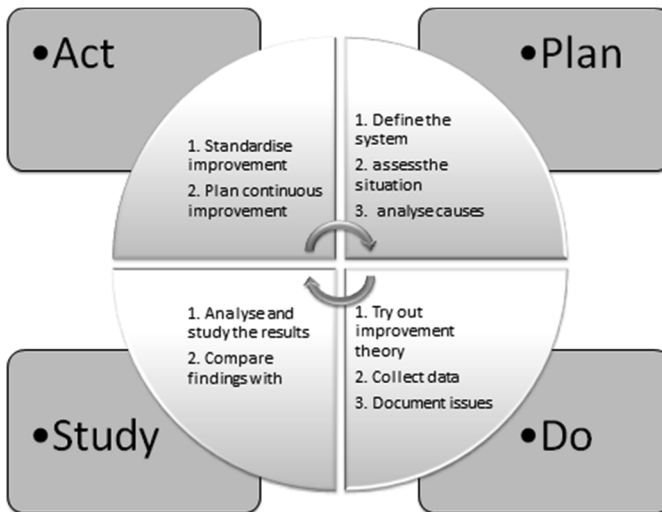


Figure 2.2. The plan do study act (PDSA) cycle for guideline implementation clinical level.

Interventions for primary vesicoureteric reflux

*A systematic review of
randomised controlled trials*

Nagler EV, Williams G, Hodson EM, Craig JC.

Interventions for primary vesicoureteric reflux.

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Abstract

Background. Vesicoureteric reflux (VUR) results in urine passing retrograde up the ureter. Urinary tract infections (UTI) associated with VUR have been considered a cause of permanent renal parenchymal damage in children with VUR. Management of these children has been directed at preventing UTI by antibiotic prophylaxis and/or surgical correction of VUR. The optimum strategy is not clear.

Objectives. To evaluate the benefits and harms of different treatment options for primary VUR.

Search methods. In August 2010 we searched CENTRAL, MEDLINE and EMBASE and screened reference lists of papers and abstracts from conference proceedings.

Selection criteria. RCTs in any language comparing any treatment of VUR including surgical or endoscopic correction, antibiotic prophylaxis, non-invasive non-pharmacological techniques and any combination of therapies.

Data collection and analysis. Two authors independently searched the literature, determined study eligibility, assessed quality, extracted and entered data. We expressed dichotomous outcomes as risk ratios (RR) and their 95% confidence intervals (CI) and continuous data as mean differences (MD) and their 95% CI's Data were pooled using the random effects model.

Main results. Twenty RCTs (2324 children) were included. Long-term low-dose antibiotic prophylaxis compared to no treatment/placebo did not significantly reduce repeat symptomatic UTI (846 children: RR 0.68, 95% CI 0.39 to 1.17) or febrile UTI (946 children: RR 0.77, 95% CI 0.47 to 1.24) at two years. There was considerable heterogeneity in the analyses and only one study was adequately blinded. At one to three years, antibiotic prophylaxis reduced the risk of new or progressive renal damage on DMSA scan (446 children: RR 0.35, 95% CI 0.15 to 0.80). Side effects were infrequent when reported, but antibiotics increased the likelihood of bacterial drug resistance threefold (132 UTIs: RR 2.94, 95% CI 1.39 to 6.25).

When long-term antibiotic prophylaxis was compared with surgical or endoscopic correction of VUR plus antibiotics for one to 24 months (10 studies, 1141 children), the risk of symptomatic UTI was not significantly different at any time point. Combined surgical and antibiotic treatment caused a 57% reduction in febrile UTI by five years (2 studies, 449 children: RR 0.43, 95% CI 0.27 to 0.70) but did not decrease the risk of new or progressive renal damage at any time point. Postoperative obstruction was seen in 0% and 7% of children in two surgical studies and 0% in one endoscopic study.

Authors' conclusions. Compared with no treatment, use of long-term, low-dose antibiotics did not significantly reduce the number of repeat symptomatic and febrile UTIs in children with VUR. Considerable heterogeneity in the analyses and inclusion of only one adequately blinded study, made drawing firm conclusions challenging. Antibiotic prophylaxis signifi-

cantly reduced the risk of developing new or progressive renal damage, but assuming an 8% baseline risk, 33 children would need long-term antibiotic prophylaxis to prevent one more child developing kidney damage over the course of two to three years.

The added benefit of surgical or endoscopic correction of VUR over antibiotic treatment alone remains unclear. Eight children would require combined surgical and antibiotic treatment to prevent one additional child developing febrile UTI by five years, but it would not cause fewer children developing renal damage.

Background

Primary vesicoureteric reflux (VUR) is thought to be a maturational abnormality of the vesicoureteric junction, which results in retrograde passing of urine up the ureter during voiding. Although the exact prevalence in children is unknown, about a third investigated after a urinary tract infection (UTI), shows signs of VUR (Smellie 1994). UTI is common, affecting 5% to 10% of all children (Hellstrom 1991), with 30% to 50% of them likely to suffer a recurrence (Smellie 1994). VUR is thought to predispose for UTI, renal involvement during UTI and hence to potentially cause subsequent permanent renal damage in 15% of patients (Montini 2007). Retrospective analyses of selected individuals with renal scarring, have reported hypertension and chronic kidney disease (CKD) in approximately 20% and 10% respectively (Martinell 1996; Smellie 1998). However recent data from a prospective cohort study have indicated, that possibly due to better treatment of acute infections, these adverse outcomes now occur considerably less frequently (Wennerstrom 2000a; Wennerstrom 2000b).

As a result of the hypothesized causal link between VUR and renal scarring, VUR screening and treatment strategies have largely been directed towards avoidance of UTI induced-damage (Belman 1995). To this end, both antibiotic prophylaxis with or without surgical VUR correction have been used. In addition to the common Politano-Leadbetter, Lich-Gregoir and Cohen surgical techniques, newer, less invasive techniques involving endoscopic periureteric injections of polydimethylsiloxane (Macroplastique), dextranomer/hyaluronic acid copolymer (Deflux) or glutaraldehyde cross-linked bovine collagen have been assessed (Capozza 2002; Frankenschmidt 1997; Frey 1997; Oswald 2002). Although VUR is a common problem in childhood, there has been no consensus regarding the optimal management strategy and practice varies widely.

Objectives

The aim of this review was to evaluate the available evidence for both benefits and harms of the currently available treatment options for primary VUR: operative, non-operative or no intervention.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) which evaluated any treatment for primary VUR were included.

Types of participants

Inclusion criteria

Males and females of any age with primary VUR diagnosed by voiding cystourethrogram (VCUG) with or without UTI.

Exclusion criteria

Patients with VUR associated with posterior urethral valves, spina bifida, other urological abnormalities or kidney transplants.

Types of interventions

Treatments of VUR including surgery (open and endoscopic techniques), antibiotic prophylaxis of any duration, non-invasive techniques such as bladder training and any combination of therapies.

Types of outcome measures

Primary outcomes

- Number of patients with symptomatic UTI, defined as symptoms consistent with a UTI together with a positive urine culture.

Secondary outcomes

- Number of patients with UTI accompanied by fever (temperature $> 38^{\circ}\text{C}$ or $> 100.4^{\circ}\text{F}$)
- Number of patients with at least one repeat positive urine culture during follow-up.
- Renal parenchymal abnormality, defined as new, progression from pre-existing damage, resolution, end-stage kidney disease (ESKD) and diagnosed by ultrasound, intravenous pyelography (IVP) or $^{99\text{mTc}}$ -DMSA (dimercaptosuccinic acid) scintigraphy (DMSA scan).
- Number of previously unaffected subjects who developed hypertension, defined as greater than 140 mm Hg systolic, 90 mm Hg diastolic for adults and above the 95th percentiles for systolic and diastolic blood pressures in children.
- Renal function impairment was defined as an estimated glomerular filtration rate (eGFR) (measured either directly or calculated from serum creatinine) less than the 95th percentile for age, or a decrease in renal function over the duration of the study.
- Correction of VUR, defined as the number of children and/or ureters without VUR on follow up VCUG.
- Microbial resistance, obstruction following correction of VUR, death or serious injury resulting from the anaesthetic, wound infection, fever, adverse effects of medication including urticaria and gastro-intestinal reaction.

Search methods for identification of studies

Initial search

Relevant studies were obtained from the following sources (see Appendix 1 for Electronic search strategies)

- The Cochrane Renal Group Specialised Register (November 2003).
 - Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Issue 4, 2003.
 - MEDLINE (1966 to February 2003).
 - EMBASE (1988 to February 2003).
 - Reference lists of relevant articles, reviews and studies.
 - Pharmaceutical industry representatives.
 - Known authors in the field.
- There were no language restrictions.

Review update search

For the first and the current update, the Cochrane Renal Group's specialised register (August 2010) and The Cochrane Central Register of Controlled Trials (CENTRAL, in The Cochrane Library Issue 8, 2010) were searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2011). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched (Renal Group 2011).

Data collection and analysis

Selection of studies

Titles and abstracts obtained from the above searches were screened for selection independently by at least two authors. In all cases an overly inclusive selection was preferred to avoid losing relevant studies and to ensure additional studies could be identified from the reference lists. Where suitability was uncertain or no abstract available, the full article was obtained and screened by the same authors. Any disagreements were resolved by discussion with a third author. Authors were contacted to obtain raw or missing data where necessary.

Data extraction and management

Data extraction was conducted independently by at least two authors, using a standardised data extraction form. All studies, reported in a non-English journal, were translated prior to assessment. Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Any disagreements were resolved by discussion with a third author.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2008) (see Appendix 2).

- Was there adequate sequence generation?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Dichotomous outcomes

For dichotomous outcomes, the risk ratio (RR) and corresponding 95% confidence interval (CI) were chosen to describe the treatment effects and the precision of their point estimates. Number needed to treat (NNT) estimates were calculated to compare the benefits and harms of each active treatment.

Continuous outcomes

Where continuous scales of measurement were used to assess effects of treatment such as blood pressure and kidney function measured by eGFR, the mean difference (MD) and 95% CI was used. Where summary statistics were missing, they were derived from accompanying P values.

Planned treatment comparisons

- Antibiotics versus surgery or endoscopic treatment
- Antibiotics versus placebo or no treatment
- One antibiotic treatment versus another
- Surgical or endoscopic correction with no other treatment
- Any combinations of any active treatment

Assessment of heterogeneity

Heterogeneity between studies was analysed using the Cochran's Q statistic with the threshold for statistical significance set at $\alpha = 0.1$ (Lau 1997). It was also tested by means of the I^2 test, reflecting the percentage of total variation across studies that could be ascribed to heterogeneity (Higgins 2003). Due to an insufficient number of studies, formal evaluation of the different sources of heterogeneity was not possible.

Assessment of reporting biases

Publication bias was to be assessed using a funnel plot; there were insufficient studies to do so.

Data synthesis

A random effects model was used, with subsequent testing for robustness of the analysis by applying a fixed effects model.

Sensitivity analysis

To determine the effect of study quality on the primary outcome's pooled summary measure, sensitivity and subgroup analysis was performed to examine the influence of allocation concealment and blinding on results.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We originally identified 10 studies after full paper assessment (Wheeler 2004). The International Reflux Study was reported in a European (IRS EUR 1981-2003) and an American arm (IRS USA 1992) and so we treated them as two separate studies. We captured two studies by screening reference lists of the authors. Both studies were published in conference proceedings only (Morris 1991; Reddy 1997). During a second search in June 2006 (Hodson 2007), we found one new study (Garin 2006) and two additional reports of the European arm of the International Reflux Study. Finally, after a search in August 2010, we included an additional nine RCTs (Craig 2002; Dite 2007; Lee 2007; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008; Scott 1968; Swedish Reflux Trial 2010). Craig 2002 was only published as an abstract and Dite 2007 was originally published in Czech and translated before assessment. We found another three papers that belonged to previously included studies (Garin 2006; IRS EUR 1981-2003; IRS USA 1992). We also identified one ongoing study (RIVUR Study), which is scheduled to finish in October 2011. See **Figure 3.1** for study selection diagram.

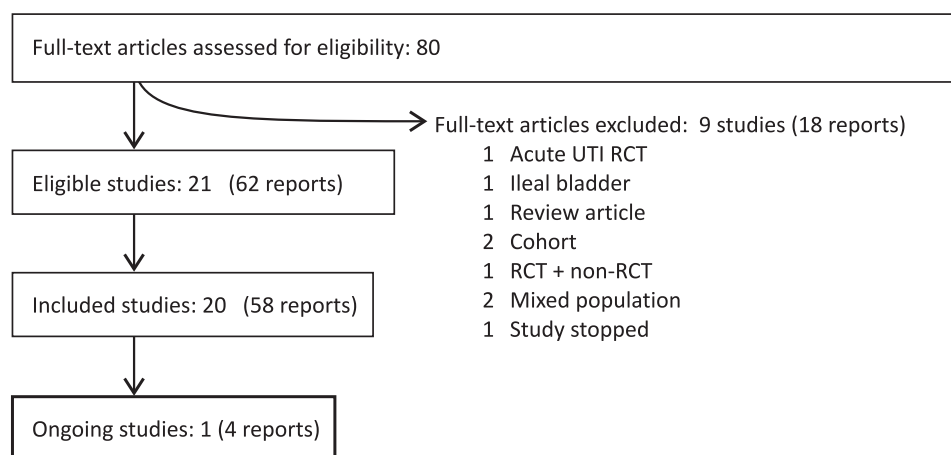


Figure 3.1. Study flow diagram.

Included studies

In eight studies (1039 children) antibiotic treatment was compared with surveillance (Garin 2006; Montini 2008; Pennesi 2006; Reddy 1997; Roussey-Kesler 2008; Swedish Reflux Trial 2010) or with placebo (Craig 2002; PRIVENT Study 2009). In most of these studies, participants were recruited after at least one symptomatic UTI (Garin 2006; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010), with subsequent exclusion of children with severe VUR, defined as grade IV (Garin 2006; Montini 2008; Roussey-Kesler 2008) or grade V (Pennesi 2006). Overall, girls outnumbered boys, with a maximum reported ratio of 4:1 (Garin 2006). In three studies (Garin 2006; Montini 2008; PRIVENT Study 2009), the investigators included both children with and without VUR. For this review, we only included the data from children with VUR. In Reddy 1997 no treatment was compared with two antibiotic prophylaxis regimens (daily or intermittent antibiotic administration). Additionally, Lee 2007 (125 children) compared probiotics with antibiotic prophylaxis. Overall the duration of the antibiotic treatment varied from one to three years.

In 10 studies (1141 children) the effectiveness of low-dose antibiotic prophylaxis, given for one to five years, was compared with ureteric reimplantation by open surgery (BIRSG 1987; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Morris 1991; Smellie 2001; Scott 1968) or endoscopic subureteric injection of Deflux (Capozza 2002; Dite 2007; Swedish Reflux Trial 2010). All who underwent a surgical or endoscopic procedure received antibiotic prophylaxis for one to 24 months, with a variety of open surgical techniques being used to correct VUR. Generally, only children with higher (dilating) grades of VUR were included. The gender distribution was usually poorly reported. Outcomes were reported at three months to 10 years post randomisation.

One study had a three-arm design (203 children), and children were randomised to endoscopic VUR correction and antibiotic prophylaxis, antibiotic prophylaxis alone, or surveillance (Swedish Reflux Trial 2010).

In two studies (88 children), researchers compared different materials for subureteric injection to correct VUR (Frey 1997; Oswald 2002). We did not find a single RCT in which an open surgical procedure was compared with endoscopic correction of VUR, nor one in which antibiotic use was compared with surgery alone, or with other treatment strategies such as management for voiding dysfunction.

In total, we have included 20 studies (58 reports) enrolling 2324 children under the age of 18 years from the USA, Europe, Australasia and South Korea. The number of participants varied between 10 and 321. Nine studies included less than 100, eight studies included between 100 and 200, and three studies enrolled more than 200 children. Data for at least one outcome was available from 2219 participants. Trimethoprim-sulphamethoxazole was the predominant chemoprophylactic drug of choice, but trimethoprim, nitrofurantoin, cefadroxil or amoxicillin-clavulanic acid were also used for antibiotic chemoprophylaxis.

Excluded studies

We excluded nine studies (18 reports). There was one acute treatment study (Montini 2003) and one study that was conducted in patients with ileal bladders (Osman 2004). There were two cohort studies (Cheskis 1995; Lindberg 1978) and one review (Becker 2004). One study was terminated before collection of outcome data because of inadequate patient recruitment (Ransley 2004). One study was omitted because it was impossible to separate the outcomes for randomised patients from those of a non-randomly selected group of children reported in the same publication (Scholtmeijer 1993). Finally both COBSG 1978 and NCBRG 1981 had included patients with and without VUR, but provided insufficient data to allow for separate analysis of the children with VUR.

Risk of bias in included studies

Before we conducted the current update, overall reporting of methodology in primary studies was generally not very detailed. In four of the most recently included studies, authors adhered to a higher standard of both design and reporting (Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008). An overview is provided in **Figure 3.2** and **Figure 3.3**.

Allocation

The method of sequence generation and treatment allocation was satisfactory in nine studies (Capozza 2002; Craig 2002; IRS EUR 1981-2003; IRS USA 1992; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Swedish Reflux Trial 2010). The other eleven used a quasi-random method or did not detail the applied procedure.

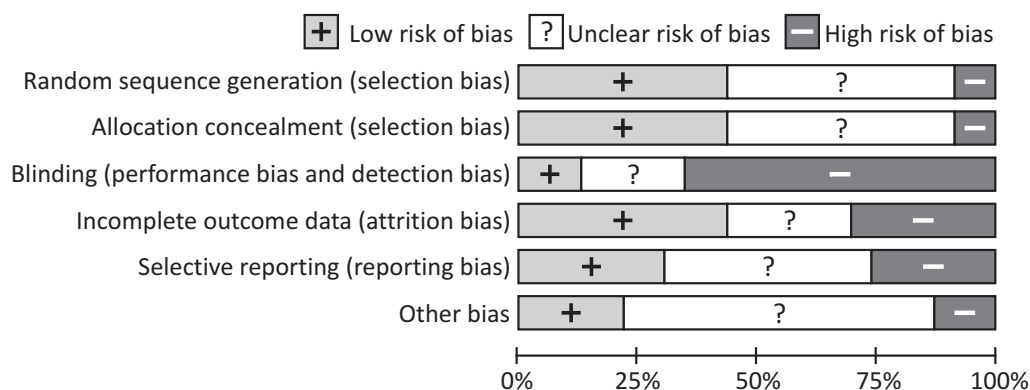


Figure 3.2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

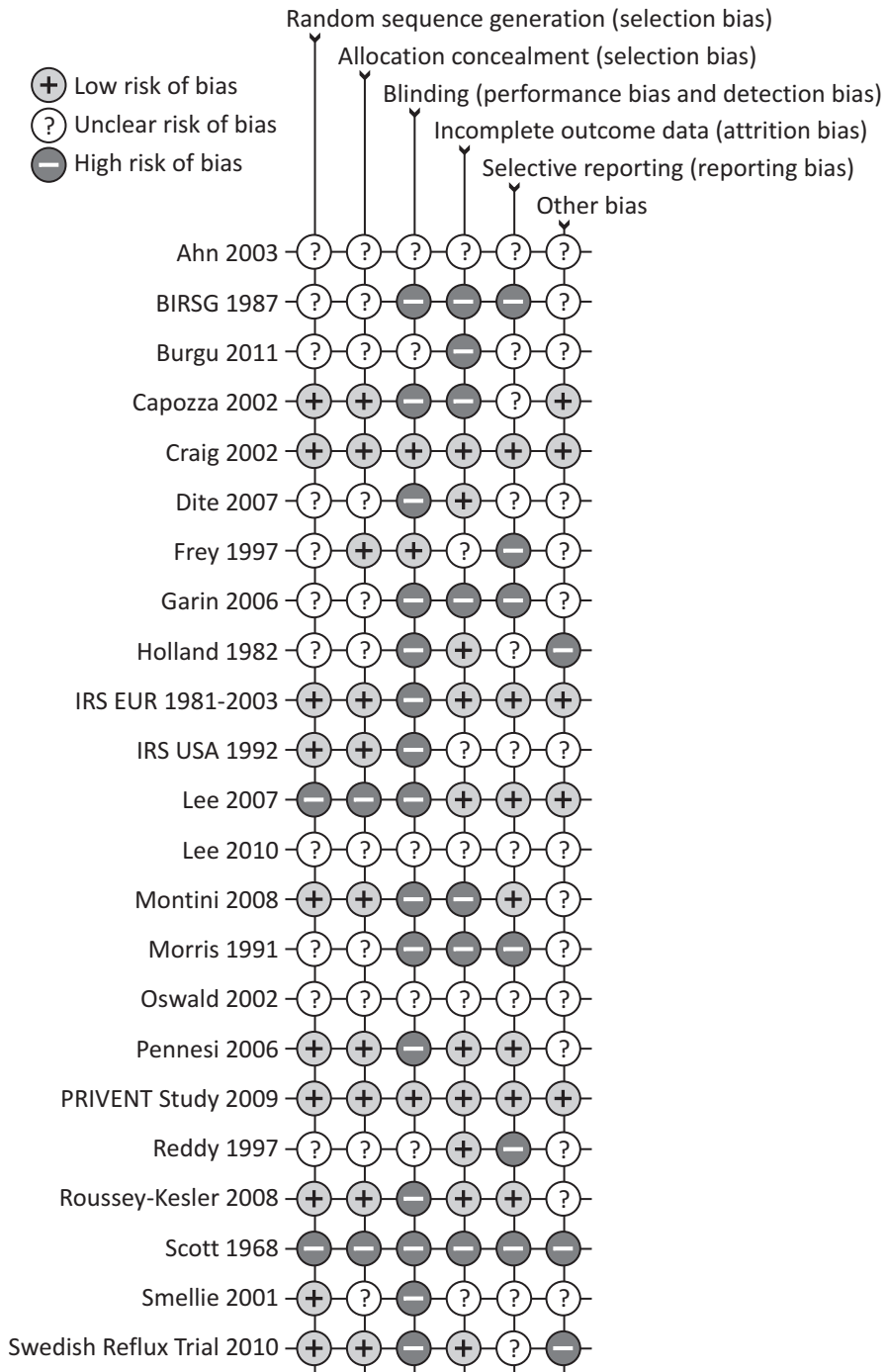


Figure 3.3. Methodological quality summary:
review authors' judgements about each methodological quality item for each included study.

Blinding

Given the nature of the intervention, blinding of investigators and participants was not possible in studies comparing the potential benefits and harms of surgical and endoscopic treatments with antibiotic prophylaxis. Yet only four explicitly reported that assessment of radiological outcomes occurred without knowledge of the treatment groups (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Swedish Reflux Trial 2010). Overall, in only three studies all participants, caregivers, outcome assessors and data analysts were adequately blinded (Craig 2002; Frey 1997; PRIVENT Study 2009).

Incomplete outcome data

Only seven studies re-included all cases for analysis that had been withdrawn during the course of follow-up (Craig 2002; Lee 2007; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010). In the remainder it was not possible to determine whether the analysis had been done on an intention-to-treat basis. Losses to follow-up over the short-term were however generally low: 0% and 10% at one to two years; 11% at three years; 5% and 42% at five to 10 years.

Selective reporting

Nine studies reported the most appropriate primary outcome, repeat symptomatic UTI (Garin 2006; Dite 2007; IRS EUR 1981-2003; Lee 2007; Montini 2008; PRIVENT Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010). Frey 1997 only described VUR correction; the other 10 described the less relevant primary outcome of repeat positive urine culture.

Other potential sources of bias

For many studies it was difficult to discern who the children were and how many were reviewed for possible inclusion in the study protocol, thereby largely limiting the ability to evaluate the extent of selection bias. Only IRS EUR 1981-2003 and PRIVENT Study 2009 clearly denoted the number of patients screened and the reasons for their exclusion or non-enrolment.

Definitions and criteria for diagnosis of initial or recurrent UTI and renal abnormalities greatly differed between the various studies and, apart from in the most recent ones, were largely inadequately reported.

Effects of interventions

Antibiotic prophylaxis versus surveillance/no treatment

The data were analysed using a random and fixed effects model, without there being an appreciable difference between the summary estimates. Results are presented using the random effects model.

Symptomatic UTI and febrile UTI

Of the eight studies that compared antibiotic prophylaxis with placebo or no treatment, six had repeat symptomatic UTI as the primary outcome and allowed distinction of febrile UTI as a separate entity. One and two year incidence of symptomatic UTI varied from 12% to 36% in the group treated with antibiotics and 2% to 41% in the surveillance group. The point estimate for overall effect favoured antibiotic prophylaxis, but the result was not statistically significant for either symptomatic UTI (Analysis 1.1.1 (5 studies, 846 children): RR 0.68, 95% CI 0.39 to 1.17) or febrile UTI by one to two years of follow-up (Analysis 1.1.2 (6 studies, 946 children): RR 0.77, 95% CI 0.47 to 1.24). For both outcomes, there was a large amount of unexplained heterogeneity among studies. We could not identify systematic differences in allocation mechanism, blinding or participant characteristics that would have explained the heterogeneity. For allocation concealment, heterogeneity appeared to be related to Garin 2006, however removing this study did not alter the statistical significance of the result (Analysis 1.2.1 (5 studies, 833 children): RR 0.69, 95% CI 0.45 to 1.05). One study was optimally designed with adequate blinding (PRIVENT Study 2009). Its point estimate again favoured antibiotic prophylaxis, but the result was not statistically significant and patient numbers were too small to give sufficient power to the analysis (Analysis 1.3).

Repeat positive urine culture

In six studies the outcome of repeat positive urine culture was reported for urine samples taken in asymptomatic subjects (Craig 2002; Garin 2006; Montini 2008; Pennesi 2006; Reddy 1997; Roussey-Kesler 2008). The analysis did not show a significant reduction in routine positive urine cultures associated with the use of antibiotics (Analysis 1.1.3 (6 studies, 636 children): RR 0.84, 95% CI 0.57 to 1.25). In addition to comparing a daily antibiotic regimen with surveillance, Reddy 1997 introduced an extra treatment arm to compare intermittent treatment three times/week, with no specific therapy. In the group treated with intermittent antibiotics 2/14 participants (14%) had a positive urine culture, in the surveillance group the culture was positive for 5/16 patients (31%) (Analysis 1.1.4 (1 study, 30 children): RR 0.46, 95% CI 0.10 to 2.00).

Renal parenchymal abnormality

In five studies, the acquisition of new renal abnormalities was evaluated by comparing DMSA scans, taken both at study commencement and completion of follow-up (Craig 2002; Montini 2008; Pennesi 2006; PRIVENT Study 2009; Swedish Reflux Trial 2010). Two studies had no events in either group and hence did not contribute to any of the analyses (Craig 2002; Pennesi 2006). Overall there was no significant reduction in either the number of children with new renal damage (Analysis 1.4.1 (5 studies, 782 children): RR 0.27, 95% CI 0.06 to 1.23) or progression of existing renal abnormalities (Analysis 1.4.2 (3 studies, 446 children): RR 0.68, 95% CI 0.27 to 1.73), although the point estimates favoured antibiotic prophylaxis in both instances. When the number of children with new or progressive renal damage were considered as a single outcome measure, the reduction was statistically significant, although only two studies contributed to the analysis (Analysis 1.4.3 (3 studies, 446 children):

RR 0.35, 95% CI 0.15 to 0.80). All physicians evaluating the DMSA scans had been adequately blinded to the treatment group and there was no substantial heterogeneity.

Two additional studies also reported development of renal abnormality but had done the baseline DMSA scan either at the time of acute pyelonephritis (Garin 2006) or not at all (Reddy 1997). In both these studies it was impossible to distinguish those who had developed the abnormality as a result of the index UTI from those in whom antibiotic prophylaxis had failed to prevent the renal damage. Overall no appreciable difference was seen in either group at one to three years when combined in meta-analysis (Analysis 1.4.4 (2 studies, 142 children): RR 1.70, 95% CI 0.36 to 8.07). Similarly, Reddy 1997 showed no meaningful difference in the risk of renal parenchymal injury between intermittent prophylaxis given three times/week and no prophylaxis (Analysis 1.4.5 (1 study, 30 children): RR 0.38, 95% CI 0.02 to 8.59).

Other outcomes

One small study (46 children), only published in abstract form, reported on estimated GFR, calculated with the MDRD equation, and renal growth at the end of a three year follow-up period (Craig 2002). Results were only reported as means, but standard deviations could be derived from the accompanying P value. Neither the difference in estimated GFR, 119 mL/min/1.73 m² in the group treated with antibiotics versus 108 mL/min/1.73 m² in the placebo group (Analysis 1.5 (1 study, 41 children): MD -11.00 mL/min/1.73 m², 95% CI -31.53 to 9.53), nor the difference in renal growth, 2.42 cm versus 2.38 cm (Analysis 1.6 (1 study, 41 children): MD 0.04 cm, 95% CI -0.04 to 0.12) was statistically significant at three years follow-up. Three studies (Pennesi 2006; Reddy 1997; Swedish Reflux Trial 2010) reported the VUR status after a two year follow-up. Overall there was no significant difference in the number of children with persisting VUR (Analysis 1.7 (3 studies, 262 children): RR 1.46, 95% CI 0.71 to 2.99).

Adherence

Adherence was addressed in 4/7 studies (Montini 2008; Pennesi 2006; PRIVENT Study 2009; Swedish Reflux Trial 2010).

- Pennesi 2006 tested the urine samples of children that developed a febrile UTI for presence of the prophylactic drug. He found all patients were compliant.
- Montini 2008 found 71% of participants were adherent when assessed by measuring antimicrobial activity in a sample of screened urine samples. The reported compliance was 86% according to the visual analogue questionnaire.
- PRIVENT Study 2009 was the only placebo-controlled study and investigators tested adherence by weighing the bottles at each clinic visit as well as by direct questioning of the parents. The authors reported no difference in the frequency of measured non-adherence between the groups. In-depth analysis of the compliance data is currently under assessment and no numeric data were available.
- The Swedish Reflux Trial 2010 report stated that adherence to the antibiotic prophylaxis had been assessed by asking questions during every follow-up visit, but no findings were

provided.

Adverse events

Only three studies reported side effects and the findings were very different for each study (Garin 2006; Montini 2008; PRIVENT Study 2009) (Analysis 1.8).

- Garin 2006 explicitly stated to have had 'no reported side effects associated with the use of urinary antibiotic prophylaxis'.
- In PRIVENT Study 2009 two participants developed thrush while on antibiotics and five developed a rash while on placebo.
- Montini 2008 reported 25 minor adverse events (out of 211 participants), mainly vomiting or gastro-intestinal intolerance. These data however included patients without VUR and were not reported per treatment group.

Microbial resistance

Four studies described bacterial resistance to the prophylactic drug in subsequent symptomatic UTIs (Pennesi 2006; PRIVENT Study 2009; Roussey-Kesler 2008; Swedish Reflux Trial 2010). Overall the estimated risk of prophylactic drug resistance in a repeat symptomatic UTI was three times higher for children that received antibiotics (Analysis 1.9.1 (4 studies, 132 urine cultures): RR 2.94, 95% CI 1.39 to 6.25). In Garin 2006, in which both frequencies of symptomatic febrile and afebrile UTIs were collected, all of the seven pyelonephritis cases in children given antibiotics were caused by a resistant micro-organism, as opposed the one case in the no treatment group which was caused by a sensitive strain. This estimate however was based on the pooled data of only three studies, with high levels of heterogeneity and imprecision due to small numbers.

Anatomic VUR correction with surgery or endoscopic injection plus antibiotics (1-24 months) versus antibiotics alone

We had planned to analyse the results of studies comparing antibiotic prophylaxis (for one to five years) with surgical VUR correction together with studies comparing antibiotic prophylaxis with endoscopic VUR correction to obtain summary measures of treatment effects. However, we separated outcomes according to follow-up time (one to two, four to five, five to 10, and more than 10 years) and for none of the time-points did the analyses include both surgical and endoscopic interventions to estimate the treatment effect. There was no appreciable difference between the summary estimates using random and fixed effects models. There were insufficient studies to explore potential effect modification using subgroup analysis or meta-regression.

Symptomatic and febrile UTI

The overall incidence of symptomatic UTI (febrile and non-febrile) was reported in three studies (Dite 2007; IRS EUR 1981-2003; Swedish Reflux Trial 2010). There was no significant difference at any time point up to 10 years between children who had undergone either surgical or endoscopic VUR correction on top of receiving antibiotics for up to 24 months

(Analysis 2.1.1 to Analysis 2.1.4). Two studies reported the number of children developing febrile UTI by two years of follow-up (Dite 2007; Swedish Reflux Trial 2010). Both were studies comparing subureteric injection of Deflux and the use of antibiotics with antibiotics alone. When combined, we found no significant difference in frequency of repeat symptomatic UTI (Analysis 2.1.1 (2 studies, 179 children): RR 0.88, 95% CI 0.26 to 3.01) or febrile UTI (Analysis 2.1.5 (2 studies, 179 children): RR 0.73, 95% CI 0.15 to 3.60). Numeric results of the individual studies contradicted each other but both studies were small and CI's wide. Both arms of the International Reflux Study (IRS EUR 1981-2003; IRS USA 1992) reported outcomes by five years of follow-up. In these studies children underwent surgical reimplantation of the ureter. After five years, there were significantly fewer children developing a febrile UTI in the group that had undergone surgery and received prophylactic antibiotics (8% to 10%) than in the group only receiving antibiotics (22%) (Analysis 2.1.6 (2 studies, 429 children): RR 0.43, 95% CI 0.27 to 0.70). The effect persisted for between five and 10 years (Analysis 2.1.7 (1 study, 252 children): RR 0.34, 95% CI 0.14 to 0.82) so that overall in children followed for 10 years there were significantly fewer febrile UTIs among children that had undergone surgical correction plus antibiotic treatment compared with children receiving only antibiotic treatment (Analysis 2.1.8 (1 study, 252 children): RR 0.54, 95% CI 0.32 to 0.92). Conversely, there tended to be fewer children with a repeat symptomatic afebrile UTI in the group treated antibiotics alone, but this result was not significant at any of the time-points.

Repeat positive urine culture

Repeat positive urine culture was examined in eight studies (BIRSG 1987; Capozza 2002; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Morris 1991; Smellie 2001; Scott 1968). The number of children with a repeat positive urine culture did not significantly differ between the group treated with antibiotics alone and the group that underwent surgical VUR correction in addition to receiving antibiotic prophylaxis at one to three years (Analysis 2.1.9 (5 studies, 388 patients): RR 0.89, 95% CI 0.55 to 1.44) and four to five years follow-up (Analysis 2.1.10 (3 studies, 479 children): RR 0.99, 95% CI 0.79 to 1.26).

Renal parenchymal abnormality

Renal parenchymal abnormalities were examined in six studies (BIRSG 1987; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001; Swedish Reflux Trial 2010). The frequency of renal parenchymal abnormality (scars and renal parenchymal thinning) on IVP at study entry was 56% to 100% with no difference between children receiving antibiotic prophylaxis alone and those treated with surgery plus antibiotics. There was no difference in the number of children developing a new renal parenchymal abnormality, either at two years (Analysis 2.2.1 (2 studies, 171 children): RR 1.06, 95% CI 0.33 to 3.42) or at four to five years (Analysis 2.2.2 (4 studies, 572 children): RR 1.09, 95% CI 0.79 to 1.49). Similarly, there was no difference in the risk of progression of an existing abnormality either at two years (Analysis 2.2.3 (1 study, 10 children): RR 7.00, 95% CI 0.45 to 108.26) or at four to five years (Analysis 2.2.4 (3 studies, 468 children): RR 0.99, 95% CI 0.69 to 1.42). When the development of a new or a progressive abnormality were considered as a single outcome at four to five

years, there was no difference between the two groups (Analysis 2.2.6 (3 studies, 468 children): RR 1.05, 95% CI 0.85 to 1.29).

The European (IRS EUR 1981-2003) and US arms (IRS USA 1992) of the International Reflux Study differentiated renal scarring and renal parenchymal thinning on IVP. There was no significant difference in the number of patients with renal scars on IVP at zero to five years (Analysis 2.3.1 (2 studies, 418 children): RR 1.28, 95% CI 0.84 to 1.94), at five to 10 years (Analysis 2.3.2 (1 study, 223 children): RR 1.03, 95% CI 0.07 to 16.22) or zero to 10 years in children followed for 10 years in the European arm of the International Reflux Study (Analysis 2.3.3 (1 study, 223 children): RR 1.03, 95% CI 0.53 to 2.00). In the IRS EUR 1981-2003, renal scarring on IVP was present at entry in 49% of the 306 children originally treated and in 51% of 223 children studied by IVP at 10 years. During the first five years of follow-up, 40 children (surgery plus antibiotic group (21); antibiotic group (19)) developed new scars. Of these, 28 were among the 223 followed radiologically at 10 years. Only two more children, one from each therapy group, developed new scars between five and 10 years.

When the data were examined according to the total number of kidneys, there were also no significant differences at two years in new (Analysis 2.4.1 (2 studies, 235 children): RR 1.03, 95% CI 0.31 to 3.37), progressive (Analysis 2.4.2 (2 studies, 235 children): RR 1.56, 95% CI 0.24 to 10.08) or total renal parenchymal abnormalities (Analysis 2.4.3 (2 studies, 235 children): RR 1.54, 95% CI 0.24 to 9.95). Similarly, the risks for new abnormality (Analysis 2.4.4 (2 studies, 319 children): RR 0.85, 95% CI 0.24 to 3.09), progression in abnormality (Analysis 2.4.5 (2 studies, 319 children): RR 0.84, 95% CI 0.50 to 1.41) or total abnormality (Analysis 2.4.6 (2 studies, 319 children): RR 0.84, 95% CI 0.53 to 1.34) did not differ at four to five years.

Two studies evaluated renal parenchymal abnormality with DMSA scan (IRS EUR 1981-2003; Swedish Reflux Trial 2010). In the Swedish Reflux Trial 2010, the number of children developing new renal damage or deterioration of already existing damage did not significantly differ between children that underwent endoscopic correction and received antibiotics versus those receiving antibiotic prophylaxis alone (Analysis 2.5.1 (1 study, 133 children): RR 2.09, 95% CI 0.66 to 6.61). In the IRS EUR 1981-2003, 97% of children had a scintigraphy performed at five years and 73% of children at 10 years. Parenchymal abnormalities were present in 83% of children at study entry. Relative to the antibiotics-only group, in the surgical plus antibiotic treatment group there was no significantly increased risk of new or progressive DMSA scan abnormalities (Analysis 2.5.2 (1 study, 287 children): RR 0.97, 95% CI 0.58 to 1.62) or of deterioration in DMSA scan appearance between five to 10 years (Analysis 2.5.3 (1 study, 216 children): RR 0.71, 95% CI 0.31 to 1.58).

Finally in Capozza 2002, renal damage was evaluated with ultrasound. There was no significant difference in the risk of abnormality at one year between medically and surgically treated participants (Analysis 2.6.1 (1 study, 81 children): RR 0.36, 95% CI 0.04 to 3.31) though only four children developed abnormalities.

Renal growth was evaluated in four studies (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) at two to 10 years by measurements of changes in renal length standard deviation score (SDS) (3 studies, 510 children) or renal area (1 study, 82 children) on IVP. No

significant differences between groups were found at any time point or in any age group. Combining data in meta-analysis as not possible because of differences in reporting.

Other outcomes

Five other outcomes were reported in 10 studies. The two outcomes of greatest clinical importance, ESKD and hypertension, were reported in three studies (BIRSG 1987; IRS EUR 1981-2003; Smellie 2001). Six children developed ESKD and 14 developed hypertension during follow-up. There was no significant difference in the risk of ESKD (Analysis 2.7.1 (2 studies, 154 children): RR 1.07, 95% CI 0.23 to 5.04) or hypertension (Analysis 2.7.2 (2 studies, 154 children): RR 0.93, 95% CI 0.25 to 3.42) between treatment groups at five years or for hypertension at 10 years (Analysis 2.7.3 (1 study, 252 children): RR 0.15, 95% CI 0.01 to 2.78).

Five studies (BIRSG 1987; Capozza 2002; IRS EUR 1981-2003; Morris 1991; Smellie 2001) reported on GFR but these were unable to be combined because of insufficiently reported point estimate and variance data. Individually, no study reported any significant difference between groups. Data from IRS EUR 1981-2003 showed no significant differences in GFR measured by the Schwartz formula at study entry (Analysis 2.8.1), at five years (Analysis 2.8.2) and at 10 years (Analysis 2.8.3).

Growth was investigated in IRS EUR 1981-2003. There was no significant difference in height SDS at study entry (Analysis 2.9.1) or at 10 years (Analysis 2.9.2).

Resolution of VUR was an outcome described in eight studies (BIRSG 1987; Capozza 2002; Dite 2007; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001; Scott 1968; Swedish Reflux Trial 2010). Combining individual study data was only possible for two studies examining endoscopic VUR correction. Unsurprisingly more children in the endoscopic group than in the antibiotics alone group had full VUR resolution after one to two years (Analysis 2.10.1 (2 studies, 164 children): RR 2.69, 95% CI 1.57 to 4.63). But assuming a spontaneous resolution rate of 15% over one to two years when treated with antibiotics alone, two to three patients would have to be treated endoscopically for one additional patient to have a response compared with antibiotic treatment alone. Capozza 2002 included VUR grade I in its definition of resolution. Still the success rate was lower than in the other two studies that evaluated endoscopic VUR correction (69% versus 38%).

We did not combine individual study data for the surgical studies, because of differences in reporting practices (patients and ureters), not all patients having had follow-up VCUGs and missing data. In four studies (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) the postoperative resolution rate at four to five years for ureters was 93% to 99%. Over a follow-up period of three to five years, 16% to 49% of patients had spontaneous resolution of VUR (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001; Scott 1968). In IRS EUR 1981-2003, 130/155 children in the antibiotics-only group had persisting VUR at five years though in 50 other children VUR grade had diminished. Among 102 children undergoing voiding VCUGs at 10 years, VUR was still present in 27 children (22 with grade IV and five with grade III). In Scott 1968, 6/31 had persistent VUR three years postoperatively and 4/31 had successful operations, but developed VUR in the opposite ureter at a later date.

Adverse events

Adverse events for either group were generally not well reported. Postoperative obstruction to the urinary tract occurred in 7% of children (10/151) in the European arm of the International Reflux Study. The Birmingham Reflux Study stated that no cases of postoperative obstruction were found after five years. None of children treated with endoscopic injection in the Swedish Reflux Trial 2010 suffered vesicoureteric obstruction. The authors did report six other adverse events. One boy had transient ureteral and renal pelvic dilatation on ultrasound at one month, one boy developed urine retention after endoscopic injection, and one boy aspirated during anaesthesia and required overnight observation in the intensive care unit. One girl suffered abdominal pain with pelvic dilatation and decreasing split function. The authors stated this resulted from a crossing vessel at the pelviureteral junction and was not related to the intervention. Finally, in one boy a fibrous narrowing of the bulbar urethra without obstruction was detected during the first endoscopic procedure. A weakening urine stream and obstructive flow curve pattern led to repeat endoscopic investigation, which revealed deterioration of bulbar narrowing. Ultimately internal urethrotomy was done. No other study referred to obstruction. No other adverse outcomes of surgery or endoscopy were reported.

*Endoscopic VUR correction plus antibiotics (minimum of three months) versus no treatment***Symptomatic and febrile UTI**

Being a three-arm study, the Swedish Reflux Trial 2010 allowed comparison of endoscopic correction versus no treatment. All children had received antibiotic prophylaxis for a period of at least three months after the endoscopic procedure when a follow-up VCUG was done. Only if this showed downgrading of the VUR status to grade I, prophylaxis was stopped. At two years follow-up, in the group who had undergone endoscopic intervention, 45% fewer children developed symptomatic UTI (Analysis 3.1.1 (1 study, 134 children): RR 0.55, 95% CI 0.33 to 0.94). Similarly, fewer children developed febrile UTI, although this result did not reach statistical significance (Analysis 3.2 (1 study, 134 children): RR 0.58, 95% CI 0.33 to 1.01).

Renal parenchymal abnormality

Although the point estimate was in favour of the combined treatment, the number of children with renal damage on DMSA scan was not significantly reduced for new damage (Analysis 3.3 (1 study, 133 children): RR 0.70, 95% CI 0.26 to 1.85), progressive damage (Analysis 3.4 (1 study, 133 children): RR 0.52, 95% CI 0.14 to 2.00) or combined new and progressive damage (Analysis 3.5 (1 study, 133 children): RR 0.70, 95% CI 0.30 to 1.60).

Other outcomes

Endoscopic treatment significantly reduced the number of children with persistent VUR at two years of follow-up (Analysis 3.6.1 (1 study, 117 children): RR 2.50, 95% CI 1.28 to 4.86). However 14 children required at least a second subureteric injection and 21% of children in

the endoscopic group did not have repeat VCUG performed at the end of the study.

Different materials for subureteric injection to correct VUR

Oswald 2002 compared endoscopic subureteric injections of Macroplastique with Deflux. Although the data seemed to indicate a lower rate of persistent VUR beyond grade I at both three months (Analysis 4.1.1 (1 study, 114 children): RR 0.48, 95% CI 0.22 to 1.04) and one year (Analysis 4.1.2 (1 study, 73 children): RR 0.62, 95% CI 0.28 to 1.40), the results were not statistically significant. Conversely, patients injected with Deflux seemed less at risk for developing afebrile UTI during follow-up, although the difference was not significant and events in both groups were sparse (Analysis 4.1.3 (1 study, 72 children): RR 1.68, 95% CI 0.52 to 5.44). Temporary pelvicaliceal dilatation however was more common following Macroplastique (Analysis 4.1.4 (1 study, 114 children): RR 1.85, 95% CI 1.02 to 3.35). No data on renal parenchymal abnormalities were reported.

One small study (Frey 1997) compared endoscopic subureteric injections of different concentrations of cross-linked collagen (GAX 65, GAX 35). VUR was five times and significantly more likely to persist following GAX 35 than GAX 65 injections (Analysis 4.2.1 (1 study, 28 children): RR 0.21, 95% CI 0.05 to 0.85). Recurrence of VUR was not significantly different between therapies (Analysis 4.2.2 (1 study, 28 children): RR 0.30, 95% CI 0.07 to 1.29). No data on UTIs or renal parenchymal abnormalities were reported.

Probiotic versus antibiotic prophylaxis

Lee 2007 compared the potential benefits and harms of probiotic versus antibiotic prophylaxis in a single centre study including 120 children. There was no appreciable difference between the two interventions in symptomatic (Analysis 5.1.1 (1 study, 24 children): RR 0.85, 95% CI 0.41 to 1.74) and febrile UTI (Analysis 5.1.2 (1 study, 24 children): RR 0.82, 95% CI 0.37 to 1.83) by one year. By the end of the one year follow-up period, 2/13 patients in the antibiotics group that had experienced a repeat UTI, had developed a new renal scar, versus 1/11 in the probiotics group. In the probiotics group, seven symptomatic UTI recurrences (64%) had *Escherichia coli* identified as the causative organism, versus nine (69%) in the antibiotics group. Whereas three of these were resistant to trimethoprim-sulphamethoxazole in the probiotic group, all of them were resistant in the antibiotic group (Analysis 5.2 (1 study, 16 children): RR 0.46, 95% CI 0.21 to 1.02).

Discussion

Summary of main results

The benefits and harms of interventions for primary VUR were assessed in 20 studies involving 2324 children.

Antibiotic prophylaxis versus surveillance/no treatment

Overall, low-dose long-term antibiotic prophylaxis tended to reduce the number of recurrent symptomatic and febrile UTIs, but the result was not statistically significant. Only one of the included studies was adequately blinded. Its point estimate favoured antibiotic prophylaxis, but the result was not significant and patient numbers too small to adequately power this analysis. Long-term low-dose antibiotic prophylaxis reduced the number of children developing new or progressive renal damage by 60% compared with no treatment. Assuming a baseline risk of 8% (Analysis 1.4.3; baseline risk 17/220), 33 children would need prophylaxis to prevent one extra child developing a new or progressive renal scar over the course of two to three years. Side effects of the preventive treatment were minor and infrequent but poorly reported. Little data were provided as to how side-effects had affected adherence. Reported compliance rates varied between 70% and 100%, but they were inconsistently measured. Since previous studies have shown poor compliance for daily antibiotic regimens for VUR (Cohen 2005; Greenfield 1997), it raises the question whether antibiotics were inherently not very effective or not being used as prescribed. Treating VUR patients with long-term low-dose antibiotics was associated with a threefold increased risk of microbial resistance against the prophylactic drug in breakthrough infection. This estimate however was based on the pooled data of only three studies, with high levels of heterogeneity and imprecision due to small numbers.

VUR correction with surgery plus antibiotics (1-24 months) versus antibiotics alone

Only the European arm of the IRS study evaluated the differential risk of symptomatic UTI between medical and surgical management. Both strategies included prescription of antibiotics, for five years or until VUR resolution in medically treated children as opposed to six months in the surgically treated children. By four to five years there was no difference in symptomatic UTI. Both the European and the American arms of the IRS study however, investigated the risk of febrile UTI and found a significant benefit for those children who underwent surgical VUR correction. Assuming a baseline risk of 22% of developing febrile UTI when on antibiotics alone (Analysis 2.1.6; baseline risk 48/218), the estimated RR of 0.43 would translate into a RD of 13% and eight patients needing surgery to prevent one extra febrile UTI over the course of five years. Further analysis at 10 years confirmed these results. It supports the idea that although surgery might not provide an added benefit over antibiotic prophylaxis in preventing symptomatic lower UTI, it might keep the infection from spreading to the upper tract, and ultimately prevent subsequent renal damage. No

evidence was found to corroborate this theory however, since the risk of developing new or progressive areas of renal damage at five and 10 years was no different between the treatment groups. You could argue that if VUR were an important modifiable risk factor for the development of UTI and renal damage, we would expect significant reduction in these outcomes for the group of surgically treated patients. It may be that delayed treatment of acute pyelonephritis is the more important risk factor, hence explaining why adverse outcomes of renal damage are currently seen less frequently than they used to (Wennerstrom 2000a; Wennerstrom 2000b). In addition, no differences between treatment groups were demonstrated for hypertension or CKD, but small numbers resulted in large imprecision and follow-up time was too short.

Potential benefits of surgery need to be weighed against its potential adverse effects. Whereas the Birmingham Reflux Study stated that no cases of postoperative obstruction were found after five years, they occurred in 7% of children (10/151) in the European arm of the International Reflux Study, corresponding to one every 14 to 15 patients undergoing the procedure.

Endoscopic treatment for VUR correction

When compared with long-term low-dose antibiotic prophylaxis alone, endoscopic correction combined with antibiotics did not significantly reduce either symptomatic or febrile UTI by two years. There was also no significant difference in new or progressive renal damage. Results however were derived from only two small studies with contradicting point estimates. When endoscopic correction was compared with no treatment in the Swedish Reflux Trial 2010, 45% fewer children developed symptomatic UTI by two years. A similar risk reduction was seen for febrile UTI, but the result was not significant. Children that underwent endoscopic VUR correction also received antibiotic prophylaxis for a minimum of three months. Given that in the comparison of endoscopic treatment versus antibiotic prophylaxis, the point estimate favoured the prophylactic treatment alone, it seems unlikely that the endoscopic treatment was responsible for the reduced risk of febrile UTI in the comparison with no treatment.

Assuming correction were beneficial, endoscopic subureteric injection of various materials could offer an alternative method of correcting VUR. It is currently widely used in North America and Europe since it is known to be associated with less pain and postoperative recovery time compared with open surgery. Four studies included in this review have demonstrated acceptable rates of VUR correction with three different materials. In a systematic review of 63 studies involving 5527 patients, the success rates for correction of VUR grades I and II, III, IV and V were 78.5%, 72%, 63% and 51% after one treatment; second treatments had an overall success rate of 68% (Elder 2006). Therefore rates of correction appeared to be lower than those reported with surgical reimplantation techniques particularly for high grade VUR.

Overall completeness and applicability of evidence

For the primary outcome of symptomatic UTI and febrile UTI, study participants had mostly lower grades of VUR. Only five participants in the PRIVENT Study 2009 had VUR grade V. These patients are generally viewed as having the highest risk of developing renal scars after pyelonephritis. Hence we should be careful with extrapolating the results from this review to children with VUR grade V. Similarly, the studies that compared surgery and antibiotics with antibiotics alone only included participants with higher degrees of VUR. This reflected the view that chances of spontaneous resolution would be slimmer and risks of renal scarring greater. VUR grade V however was also excluded from the International Reflux Study, since it was regarded to be part of a widespread malformation of the urinary tract instead of an isolated problem of the vesicoureteric junction and thought to experience a greater benefit from surgery.

A randomised comparison between antibiotic treatment and surgery alone has not been performed since in all studies, antibiotics were also given for a variable length of time. Only studies designed to assess the incremental benefit of surgery over antibiotics alone have been conducted.

Quality of the evidence

The quality of conduct and reporting of these studies was variable, with many studies omitting crucial methodological information used to assess the risk of bias.

This review update has mainly added new studies that compared antibiotics to no treatment. Although in general both methodological quality and standard of reporting were good, only the PRIVENT Study 2009 was optimally designed, providing placebo and ensuring blinding of all participants, caregivers, outcome assessors and data analysts.

The effect estimate of incremental benefit of surgery was based on only one study that included 429 patients in the analysis. Given the nature of the intervention, it was not possible to blind participants or healthcare providers. Since this tends to result in overestimation of the treatment effect (Schulz 1995), bias might have played a part in producing the statistically significant difference in febrile UTI in favour of surgical management.

Agreements and disagreements with other studies or reviews

For over five decades, scientific published work has suggested the existence of a link between recurrent UTI, VUR and renal scarring (Olbing 2003; Smellie 1975; Smellie 1994; Smellie 1998). VUR has been thought to facilitate the involvement of the upper urinary tract during UTI by allowing retrograde passage of infected urine to the ureter. Subsequently all interventions have been targeted at preventing UTI-induced damage to the kidney. Earlier versions of this review (Hodson 2007; Wheeler 2004) were not able to provide evidence as to whether the common practice of diagnosing and treating children with VUR conferred important health benefits, since no adequately powered studies had included a no treatment arm. Five new studies have since been published that compare the adminis-

tration of antibiotics with placebo or no treatment. Although the addition of these studies produced a risk estimate in favour of long-term low-dose antibiotics, the result was not statistically significant. Only one of studies was optimally designed with adequate blinding of all participants and personnel involved in the study (PRIVENT Study 2009). When analysed by itself it produced a RR of 0.70. The result was not significant (95% CI 0.35 to 1.24), but patient numbers too small to adequately power the analysis. In the original study, the investigators had included 576 children both with and without VUR. They found a 6% absolute risk reduction (95% CI 1 to 13) for the group treated with antibiotics versus those treated with placebo and the effect of preventive antibiotic treatment did not differ according to the VUR status.

In comparison to the previous review, we have highlighted symptomatic and febrile UTI as more relevant primary end points rather than positive urine cultures.

Authors' conclusions

Implications for practice

Compared with no treatment, use of long-term low-dose antibiotics tended to reduce the number of repeat symptomatic and febrile UTIs in children with VUR, but the result was not statistically significant. A large amount of unexplained heterogeneity in the analysis and inclusion of only one adequately blinded study, makes drawing firm conclusions challenging. Prophylaxis modestly reduced the risk of new or progressive renal damage, produced few side effects but was associated with a threefold increase in prophylactic drug resistance in subsequent UTIs.

The added benefit of surgery over long-term low-dose antibiotic use remains uncertain. Although there was a significant reduction in repeat episodes of febrile UTI, there were no differences in either symptomatic UTI or renal damage. Informed decision making should consider the risk of adverse events associated with surgery. Correcting VUR using endoscopic approaches would theoretically reduce these risks it but was not associated with a reduced number of symptomatic or febrile UTIs or a reduction in new or progressive renal damage.

Implications for research

We still need a well-designed, blinded and adequately powered study in children with VUR to resolve the remaining uncertainty surrounding the benefit of antibiotic prophylaxis in preventing UTI and renal damage. Hence we await with interest the results of the ongoing, placebo-controlled 'randomised Intervention for children with VesicoUreteral Reflux' study (RIVUR Study), which examines the effect of low-dose antibiotic treatment on symptomatic UTI and renal parenchymal injury assessed by DMSA scan. The role of surgery in the management of VUR needs further exploration. Of specific interest would be the impact of VUR correction by endoscopic subureteric injection without antibiotics versus no treatment

on the incidence of febrile UTI and renal parenchymal injury assessed by DMSA scan.

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Characteristics of studies

Characteristics of included studies

See online version of the publication

Data and analyses

See online version of the publication

**Antidepressants for depression in
stage 3–5 chronic kidney disease**
*a systematic review of pharmacokinetics,
efficacy and safety with recommendations
by European Renal Best Practice (ERBP)*

Nagler EV, Webster AC, Vanholder R, Zoccali C.

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Abstract

Background. The prevalence of major depression in stage 5 chronic kidney disease (CKD) varies between 14 and 30%. Patients with CKD who are depressed have a worse quality of life, are hospitalized more often and die sooner than those who are not depressed. Antidepressant drugs are effective in the general population, but whether they improve outcomes in CKD is uncertain. Drug pharmacokinetics are altered in CKD, which may necessitate dose adjustment. We aimed to systematically review available evidence of the pharmacokinetics, efficacy and safety of antidepressant drugs when used in patients with CKD3 to CKD5 (CKD3-5).

Methods. This is a systematic review of randomized clinical trials and observational studies examining antidepressants in patients with CKD3-5, regardless of whether or not patients are on dialysis. Through comprehensive searches of seven databases, we identified all studies examining pharmacokinetic properties or clinical outcomes in patients with CKD3-5. One author assessed studies for eligibility and quality and extracted all data. Antidepressant drugs were the studied intervention. The main outcomes were pharmacokinetic parameters, clinical outcomes such as response to treatment, reduction in depression severity and adverse events.

Results. We identified 28 studies evaluating pharmacokinetic parameters in CKD for 24 antidepressants. Sparse and heterogeneous data precluded informative meta-analysis. Drug clearance in CKD3-5 was markedly reduced for selegiline, amitriptylinexide, venlafaxine, desvenlafaxine, milnacipran, bupropion, reboxetine and tianeptine. We identified one randomized controlled trial (RCT) in 14 patients on haemodialysis for fluoxetine versus placebo which showed no difference for efficacy and safety measures. One other RCT of escitalopram versus placebo in 62 patients on haemodialysis provided no efficacy data. There were nine non-randomized trials, all suggesting benefit for the antidepressant under investigation. Side-effects were common, but mild in most patients. The limitations of this review include the scarcity of randomized trial data, the small size of the observational studies and possibility of publication bias. In addition, study selection and data extraction were done by one reviewer only, increasing the risk for errors made in handling of the data.

Conclusions. Dose reduction in CKD3-5 is necessary for selegiline, amitriptylinexide, venlafaxine, desvenlafaxine, milnacipran, bupropion, reboxetine and tianeptine. The evidence on effectiveness of antidepressants versus placebo in patients with CKD3-5, and with the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)-defined depression is insufficient, and in view of the high prevalence, a well-designed RCT is greatly needed.

ERBP Recommendations

- 1.1 We suggest that in patients with CKD3 to CKD5 (CKD3-5) who meet DSM-IV criteria for moderate major depression, active treatment is started (2D).
- 1.2 We suggest a trial with antidepressant drug therapy can be started. After 8–12 weeks, the treatment effect should be re-evaluated to avoid prolonging ineffective medication (2D).
- 1.3 We suggest using a selective serotonin re-uptake inhibitor as a first-line agent, if treatment with an antidepressant drug is considered (2C).

Rationale

A recent Cochrane review on antidepressant drug therapy in the physically ill showed antidepressants to be significantly more effective than placebo (odds ratio 2.33, 95% confidence interval 1.8–3, number needed to treat = 6) [1]. For patients with CKD3-5, we identified only one published randomized trial in 14 patients, which did not suggest a beneficial effect of antidepressant drugs. Nine reports of prospective non-controlled studies that evaluated the effect of antidepressant drugs in CKD [2–10] found a benefit for the antidepressant under investigation, yet effect estimates were of similar magnitude for the placebo effect found in the one randomized controlled trial (RCT). As such, there is insufficient evidence for a general recommendation to routinely use an antidepressant agent in patients with CKD3-5 and a DSM-IV-defined depression. However in line with the current treatment guidelines, the high prevalence of depression in patients with CKD3-5 and its negative influence on survival and quality of life, active intervention seems justified. Given the very mild side effects of the studied antidepressants in CKD 3-5, an 8–12-week trial with these drugs can be considered in patients suffering from moderate depression according to DSM-IV [11]. However, the overall poor reporting of side-effects in trials in addition to observational data suggesting an association with increased risk of falls in elderly patients [12], means one should be careful when balancing the potential benefits against their potential harms. In any case, the effectiveness of the treatment should be evaluated after the initial 8–12-week treatment phase and the drug should be withheld when no benefits observed.

Non-pharmacological treatments might provide equal benefit, without the potential harms and can represent valuable alternatives to antidepressant drug therapy. As they were not studied in this review, we refrained from making any statements. Of all the clinically studied compounds in patients with (CKD3-5), all but one belong to the class of selective serotonin reuptake inhibitors. Hence, from an evidence-based viewpoint, it seems reasonable to advocate the use of these agents as the first-line treatment of choice.

Introduction

Major depression is diagnosed when symptoms of persistent unreactive mood and loss of all interest or pleasure are accompanied by insomnia, fatigue, lethargy, loss of energy or appetite, poor concentration, restlessness, inappropriate guilt and/or morbid thoughts of death [13]. With an estimated prevalence of 14–30%, major depression is the most common psychological problem in patients with stage 5 chronic kidney disease (CKD5) [14–16].

Aside from having a worse quality of life, depressed patients with CKD are hospitalized more often and die sooner than those who are not depressed [16–18]. Proposed causal mechanisms to explain these poor outcomes include inflammation as well as non-adherence to therapy, an unhealthy lifestyle and poor nutrition [16]. It is reasonable to assume that successfully treating depression would improve overall wellbeing in these patients, but whether it will lead to better survival is uncertain.

Antidepressants are effective in treating depression in the general population [19, 20]. Around 50–65% of patients have reduced symptoms when treated with antidepressants compared with 25–30% when treated with placebo [20]. Improvement is usually observed within the first 3 weeks of starting therapy, but can take up to 6 weeks to become apparent.

Antidepressant drugs act by increasing the activity of one or more of the neurotransmitters serotonin, nor-adrenaline and/or dopamine in the central nervous synapses, by either preventing their enzymatic breakdown in the synaptic cleft, inhibiting re-uptake across the presynaptic cellular membrane, stimulating release from the pre-synaptic cells or stimulating effects on the postsynaptic receptor.

CKD may affect antidepressant pharmacokinetics unpredictably for several reasons. Impaired kidney function decreases drug excretion, but may also lead to reduced intestinal availability by slowed gastric emptying. Drug accumulation may result from altered absorption or hepatic metabolism and protein binding may differ according to the acidity of the drug [21]. Finally, dialysis may remove a drug to such extent that a substitution dose is needed to preserve the desired effect [22]. As a result, dose adjustments based on data from the general population and the expected influence of renal impairment may be highly inaccurate.

In a recently updated Cochrane review on the use of antidepressants in the physically ill, Rayner et al. [23] identified only two small randomized, placebo controlled trials, conducted in, respectively, 14 and 62 patients with CKD5 [24, 25]. We are not aware of any previous attempts to systematically summarize the pharmacokinetic data.

Given these uncertainties, we aimed to identify antidepressant compounds that might need dose adjustments in CKD3-5 and to identify both the benefits and harms of antidepressant medications in the management of CKD3-5 patients with depression.

Materials and methods

Criteria for considering studies for this review

We considered all study types in which an antidepressant drug was studied prospectively in humans. Neither randomized allocation nor a non-randomized control group was considered an absolute prerequisite, and we imposed no restrictions based on the number of participants in each trial. Because rare but potentially life-threatening side-effects are not necessarily captured by trials, we included all reports of serious adverse events, regardless of study design.

We included studies enrolling adults or children with CKD stage 3 (CKD3), 4 (CKD4) or 5 (CKD5) as defined by the KDOQI guidelines [26]. That is, we included all patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m² of body-surface area, calculated using the Modification of Diet in Renal Disease formula or any other glomerular filtration rate estimation equation. For trials evaluating the efficacy of an antidepressant, we required participants to have a diagnosis of depression, although we did not specify the diagnostic tools used to make the diagnosis. We excluded trials in which antidepressants were prescribed primarily to treat symptoms other than depression.

All drug compounds listed as antidepressants according to the British National Formulary [27], the American Hospital Formulary Service Drug Information [28] or the Dutch Farmacotherapeutisch Kompas [29] were eligible for this review (**Table 4.1**). We excluded mood-stabilising drugs such as lithium, even if they had been used to treat depression.

The first outcome category consisted of basic pharmacokinetic parameters reflecting the different aspects of absorption, bioavailability, drug distribution, metabolism and excretion (Table 4.2). The second category comprised measures of efficacy and harm. Here, the main outcomes were response to treatment, improvement upon treatment and change in depression severity as defined by the investigators and according to whatever scale they used. We also looked at hospitalization rate, all-cause mortality, suicide or suicide attempts, withdrawal from dialysis, adherence to treatment for CKD, quality of life and effect on nutritional parameters. An attempt was made to report on adverse events attributable to the antidepressant intervention as a measure of tolerability and the number of dropouts from the antidepressant therapy as a proxy of acceptability.

Search methods for identification of studies

The search strategies we used to retrieve studies from the bibliographic databases combined medical subject headings and text words for CKD, end-stage renal disease, depression and antidepressants, limiting to studies conducted in humans. We did not apply a methodological filter nor did we impose any restriction on language. The search strategies are detailed in Supplementary Appendix 1.

To identify studies for inclusion in this review, in December 2011, we searched The Cochrane Renal Group Specialized Register, CENTRAL in the Cochrane Library, MEDLINE

from 1950, EMBASE from 1980, PsychINFO from 1967, International Pharmaceutical Abstracts from 1950, Clinical trial registries endorsed by the International Committee of Medical Journal Editors, reference lists of nephrology textbooks, pharmaceutical reference works, review articles and relevant studies.

Data collection, extraction, analysis and assessment of risk of bias

Both initial screening of all titles and abstracts, subsequent full-paper assessment of potentially eligible studies and extraction of the data from included studies was done by E.V.N. All studies reported in a language other than English were translated before assessment. Additional data were requested from authors for the randomized controlled trials (RCTs) only.

The quality of the included studies was assessed by E.V.N., without blinding to authorship or journal. We did not formally evaluate the risk of bias in the pharmacokinetic studies, as no validated tool exists. Instead, we described the process for participant selection, participant characteristics, completeness of outcome reporting, addressing of all active metabolites, reporting of analytic procedures and mathematical model building. For randomized trials describing efficacy, we used the risk of bias checklist as recommended by the Cochrane handbook for systematic reviews on interventions [30]. For non-randomized or uncontrolled trials and observational studies, we highlighted the design features that may introduce bias [31].

Data reporting

We reported both pharmacokinetic and clinical results in tables (See Supplementary Appendix 2 and 3). Sparse and heterogeneous data precluded informative formal meta-analysis. For many drugs, not all pharmacokinetic parameters were known for individuals with renal impairment. In such cases, drug disposition was predicted from knowledge of the drug's pharmacokinetics in patients with normal kidney function. Hence, we provided data generated in the general population, retrieved from six reference works [27–29, 32–33] and supplemented this with data from studies conducted specifically in patients with CKD.

For pharmacokinetic data, we presented findings as continuous data with measures of central tendency and distribution as reported by the original authors. We reported exact P-values where possible.

For efficacy measures, we reported categorical data in absolute numbers. For controlled trials, we had planned to supply the results in terms of relative risks and their 95% confidence interval (95% CI). Both of the two identified controlled trials, however, reported results only on a continuous scale. We reported these results as a mean difference and 95% confidence interval when possible. For uncontrolled trials, findings were reported as change from baseline or as group means at beginning and end of the trial. Standard deviations were supplied where possible. If significance tests had been conducted, mean change from baseline, 95% confidence intervals and P-values were reported as in the original article. If standard errors

Table 4.1. Suggested Dosing Scheme with normal and impaired renal function.

Class	Dose in normal renal function	Dose in eGFR 30-60 ml/min	Dose in eGFR 15-30 ml/min	Dose in eGFR <15 ml/min	Dose in RRT (HD, PD and HDF)
Monamine Oxidase Inhibitor					
Isocarboxacid	30-60 mg daily in single or divided doses	No adjustment	No adjustment	No adjustment	No adjustment
Phenelzine	45-90 mg daily in three divided doses	No adjustment	No adjustment	No adjustment	No adjustment
Prasidol	No information	No data	No data	No data	No data
Tranylcypromine	30-60 mg daily in two divided doses, morning and early afternoon	No adjustment	30 mg, increase carefully	30 mg, increase carefully	30 mg, increase carefully
Selegiline	5-10 mg daily in single or divided doses	5 mg, increase carefully*	5 mg daily*	5 mg daily*	5 mg daily
Tricyclic Antidepressants					
Clomipramine	10-250 mg daily, single or divided doses	No adjustment	10 mg, increase carefully	10 mg, increase carefully	10 mg, increase carefully
Desipramine	25-300 mg daily, single or divided doses	No adjustment	No adjustment	25 mg, increase carefully	25 mg, increase carefully*
Lofepamine	140-210 mg daily, two-three divided doses	No adjustment	No adjustment	140 mg, increase carefully	140 mg, increase carefully
Nortriptyline	30-150 mg daily, single or divided doses	No adjustment*	No adjustment*	No adjustment*	No adjustment*
Amitriptyline	75-200 mg daily, single dose	No adjustment	No adjustment	No adjustment	No adjustment*
Amitriptylinoxide	30-300 mg daily	No adjustment	15 mg, increase carefully	15-150 mg daily	15-150 mg daily
Dibenzepine	240-720 mg daily	No adjustment	240 mg, increase carefully	240 mg, increase carefully	240 mg, increase carefully
Dosulepine	75-225 mg daily, max single dose 150 mg	No adjustment	75 mg, increase carefully	75 mg, increase carefully	75 mg, increase carefully
Doxepine	10-300 mg daily, max single dose 100 mg	No adjustment	No adjustment	No adjustment*	No adjustment*
Imipramine	10-200 mg daily, single or divided doses	No adjustment	10 mg, increase carefully	10 mg, increase carefully*	10 mg, increase carefully*
Melitracen	25-225 mg daily, two-three divided doses	No data	No data	No data	No data
Protriptyline	15-60 mg daily, single or divided doses	No adjustment	15 mg, increase carefully	15 mg, increase carefully	15 mg, increase carefully
Mianserin	30-90 mg daily, max single dose 60 mg	30 mg, increase carefully	30 mg, increase carefully	30 mg, increase carefully	30 mg, increase carefully
Amoxapine	75-400 mg daily, single or divided doses	No adjustment	No adjustment	No adjustment	No adjustment
Maprotiline	50-200 mg daily, single or divided doses	No adjustment	50 mg, increase carefully*	50 mg, increase carefully	50 mg, increase carefully*
Selective Serotonin reuptake Inhibitor					
Citalopram	10-40 mg daily in single dose	No adjustment*	No adjustment*	No adjustment*	No adjustment*
Escitalopram	10-20 mg daily in single dose	No adjustment	10 mg, increase carefully*	10 mg, increase carefully	10 mg, increase carefully
Fluvoxamine	50-300 mg daily, max single dose 150 mg	No adjustment	No adjustment	No adjustment	No adjustment*
Fluoxetine	20-60 mg daily, in single dose	No adjustment*	No adjustment*	No adjustment*	No adjustment*
Paroxetine	20-50 mg daily, in single dose	10 mg, increase carefully*	10 mg, increase carefully*	10 mg, increase carefully*	10 mg, increase carefully*
Sertraline	50-200 mg daily in single dose	No adjustment	50 mg, increase carefully	25 mg, consider reducing max dose	25 mg, consider reducing max dose

Table 4.1. (continued)

Class	Dose in normal renal function	Dose in eGFR 30–60 ml/min	Dose in eGFR 15–30 ml/min	Dose in eGFR <15 ml/min	Dose in RRT (HD, PD and HDF)
Serotonin Norepinephrine Reuptake Inhibitor					
Venlafaxine	75–225 mg daily, three divided doses	No adjustment	37.5–112.5 mg	37.5–112.5 mg	37.5–112.5 mg*
Desvenlafaxine	50 mg daily, single dose	25 mg, increase carefully*	25 mg daily*	25 mg daily*	25 mg daily*
Duloxetine	40–120 mg daily, single or divided doses	No adjustment	40 mg, increase carefully*	40 mg, increase carefully*	40 mg, increase carefully*
Milnacipran	50–100 mg daily, two divided doses	25 mg, increase carefully*	25–50 mg*	25–50 mg	25–50 mg
Serotonin Modulator					
Nefazodone	100–600 mg daily, two divided doses	100 mg, increase carefully*	100 mg, increase carefully*	100 mg, increase carefully*	100 mg, increase carefully
Trazodone	150–600 mg daily, divided doses	No adjustment*	No adjustment*	150 mg, increase carefully*	150 mg, increase carefully
Noradrenergics and Specific Serotonergics					
Mirtazapine	15–45 mg in single or two divided doses	No adjustment	15 mg, increase carefully	15 mg, increase carefully*	15 mg, increase carefully*
Norepinephrine Dopamine Reuptake Inhibitors					
Bupropion	200–450 mg, max single dose 150 mg	150 mg daily*	150 mg daily*	150 mg daily*	150 mg daily*
Dopamine Receptor agonist					
Trimipramine	50–300 mg daily, max single dose 200 mg	No adjustment	No adjustment	50 mg, increase carefully*	50 mg, increase carefully
Reversible MAO-inhibitor					
Moclobemide	300–600mg daily, in three divided doses	No adjustment*	No adjustment*	No adjustment*	No adjustment*
Selective Serotonin Reuptake Enhancer					
Tianeptine	25–37.5 mg daily in two-three divided doses	12.5 mg, increase carefully	12.5–25 mg*	12.5–25 mg*	12.5–25 mg*
Melatonergic antidepressant					
Agomelatine	25–50 mg daily in single dose	No adjustment	No adjustment	No adjustment	No adjustment
Selective Norepinephrine Reuptake Inhibitor					
Reboxetine	8–12 mg daily in two-three divided doses	4–6 mg daily*	4–6 mg daily*	4–6 mg daily*	4–6 mg daily
Viloxazine	200–600 mg, divided doses	Not studied	Not studied	Not studied	Not studied

Dose suggestions are based on extrapolated and/or indirect data only, unless marked with *

Table 4.2. *Types of pharmacological outcome measures.*

Symbol	Full	Unit of measurement
M	Molecular Mass	d, g/mol
A	Degree of absorption from gastro-intestinal tract	Qualitatively, % of total oral dose
F	Bioavailability	% of intravenous dose reaching systemic circulation
C _{max}	Peak plasma concentration	ng/ml
t _{max}	Time to peak plasma concentration	hours
Vd	Apparent distribution volume	L or L/kg
PPB	Degree of plasma protein binding	% of total plasma concentration
AUC	Area under the curve	unitless
t _½	Elimination half-life	Hours
CL/F	Plasma clearance after oral administration as calculated from the area under the curve in a plasma concentration time curve	L/h
CL _r	Plasma clearance by the kidney	L/h
CL _d	Plasma clearance by dialysis	L/h

were not available, attempts were made to calculate the 95% confidence interval from exact P-values if they were available.

Results

Pharmacokinetics

Characteristics of included studies

We identified 33 published reports [2, 3, 21, 35–64] of 28 studies investigating pharmacokinetic parameters for 24 antidepressant medications. (**Figure 4.1**) Twelve studies exclusively included patients with CKD5 treated either with peritoneal dialysis [50, 60] or haemodialysis [2, 3, 45, 47, 50, 51, 55, 57, 58, 61, 63]. One study included only patients with CKD5, who were not yet on dialysis [45]. Another study included patients with CKD4 and CKD5 treated either conservatively or with haemodialysis [53, 54]. Thirteen studies also included patients with CKD3 [35, 38, 40–43, 46, 48, 49, 56, 59, 62, 64], and in three, it was not possible to distinguish between CKD3 and more advanced CKD [21, 35, 48]. Finally, we accepted one study that had included one patient with CKD2 as well as two with CKD3 and five with CKD4, where individual patient data could not be extracted [52].

Four trials only looked at drug removal through dialysis [3, 45, 55, 57]. Two were in vitro studies of plasma protein binding [21, 52]. The 21 others were full pharmacokinetic studies, but reported outcomes incompletely [2, 35–44, 46–50, 52–54, 56, 58–64].

Of the 21 pharmacokinetics studies, five reported six of the nine pre-specified outcome measures [21, 41, 48, 61, 64], five reported five [36, 49, 53, 54, 56, 58, 59, 63], six reported four [39, 44, 62] or three [35, 37, 38, 46], and three reported two [42, 43, 47] or one [60] (**Table 4.2**).

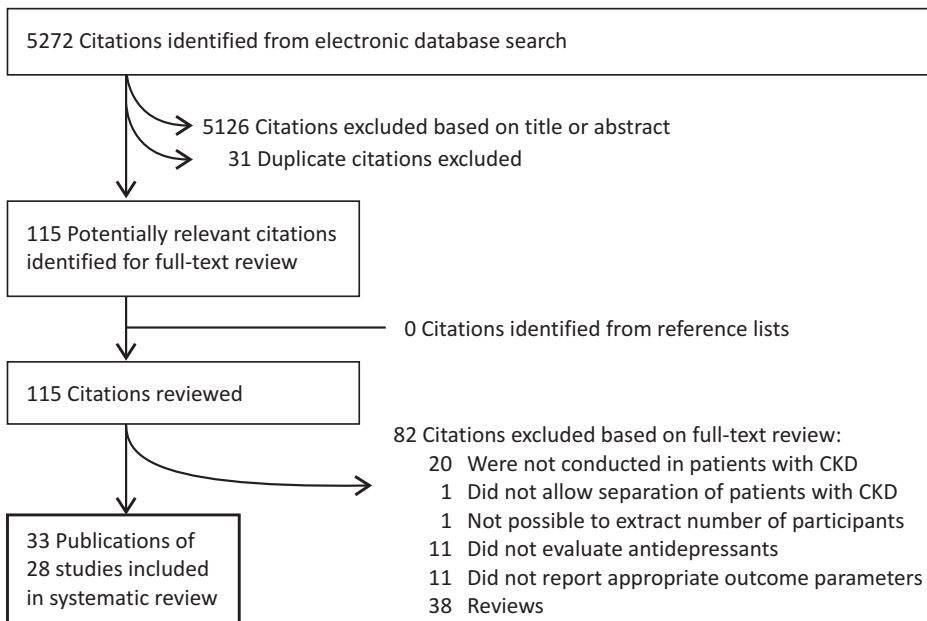


Figure 4.1. Selection process for inclusion of studies in review of pharmacokinetics.

Finally, three studies only reported serum concentrations of the drug under investigation [2, 40, 50].

On average, the number of participants with CKD in each trial was small. Only three studies included >20 patients [21, 51, 64], 12 included between 11 and 20 [36–44, 46, 49, 50, 53, 54, 56, 59], 11 included between 2 and 10 [2, 3, 35, 47, 48, 52, 57, 58, 60, 62, 63], and 2 only included 1 patient [45, 55].

Fourteen studies mentioned inclusion or exclusion criteria. Only seven stated them explicitly [2, 36, 39, 49, 56, 59, 61, 63, 64]. Of the 19 trials that included dialysis patients, nine detailed both the frequency and duration of the dialysis procedure and the type of dialyser or the dialysis solutions used [21, 42, 43, 47, 51, 57, 58, 60, 61, 63]. Two studies provided details about frequency and duration only [3, 50].

No study clearly described the selection process. Underlying renal disease was explicitly reported in nine trials [40, 42, 43, 47–50, 58–60, 63], but only three studies detailed other comorbidities [2, 51, 57], and only eight listed other medications patients were chronically taking [35, 42, 43, 45, 50, 51, 57, 60, 63].

Of 23 trials needing control groups (all but the four dialysis studies), only five trials presented inclusion and/or exclusion criteria for controls [2, 48, 61, 62, 64]. Characteristics were generally poorly described. Age, sex and/or body weight were provided by 16 studies [2, 35–39, 42–44, 48–52, 58, 60, 62, 64].

Three trials studied both single and multiple dosing [40, 42, 43, 58]. In the 24 others, authors limited analyses to only single [21, 35, 38, 39, 41, 44, 46–48, 51–54, 56, 57, 59–64] or

multiple dosing [2, 3, 37, 45, 50].

Of the 21 studies that should have addressed the pharmacokinetics of the active metabolite [2, 21, 35–37, 40–45, 47, 49, 51, 53–57, 59–63], only 15 did so [2, 35–37, 42–44, 47, 49, 51, 53–56, 59, 61–63]. The others only discussed the parent drug.

Analytic procedures used to measure drug concentrations were detailed in 21 trials [2, 21, 35, 37–39, 41–44, 48, 50–52, 56–64]. Only limited detail was given in seven trials [36, 40, 46, 47, 49, 53–55]. One did not mention them at all [56].

Of the 21 full pharmacokinetic studies, 17 described mathematical model building. Two allowed for non-linear kinetics [49, 64], whereas all others assumed a one-compartment model or linear kinetics [35, 37–39, 42–44, 46, 52–54, 56, 58–62, 64].

Findings

Drug elimination was studied in patients with CKD3-5 including haemodialysis patients on a non-dialysis day. Elimination half-life was importantly prolonged and/or drug clearance markedly reduced after oral intake for amitriptylinexide [44], venlafaxine [61], desvenlafaxine [64], milnacipran [52], bupropion [62] and reboxetine [41]. For selegiline, the elimination half-life could not be reliably calculated but the area under the plasma concentration curve was significantly increased [50]. Mirtazapine had a reduced plasma clearance after oral intake, but not a prolonged elimination half-life [55].

For tianeptine neither elimination half-life nor clearance after oral intake was different for the parent compound [53, 54]. However, the elimination half-life of its active metabolite was markedly increased [53, 54]. For imipramine [50], sertraline [57] and nefazodone [38], on average the half-life was importantly increased numerically, although in these small and underpowered studies none of the differences in half-life were significant when compared with healthy controls. For amitriptyline [60], doxepine [47], citalopram [48, 58], fluoxetine [36, 49], trazodone [40] and moclobemide [56, 59], the various pharmacokinetic parameters were similar between patients with advanced CKD and healthy controls. Interindividual variability of parameters was high in all trials.

Removal by haemodialysis was directly tested for nine compounds during a 4-h session with a low-flux dialyser. For fluvoxamine, there was an average 21% reduction in its plasma concentration during the dialysis session in three patients under evaluation [3]. Only limited amounts of desipramine [50], nortriptyline [42], amitriptyline [60], doxepin [47], citalopram [58], fluoxetine [49], venlafaxine [61], trazodone [45] and mirtazapine [55] were removed by dialysis. Drug removal was only assessed for patients undergoing standard haemodialysis. No information was identified for the more efficient strategies such as high-flux dialysis, haemodiafiltration and daily or long dialysis. There was no specific information on removal by peritoneal dialysis.

The potential need for a dose increase in patients on haemodialysis was evaluated in two studies. For two patients treated with amitriptyline, the elimination half-life was similar to that in the general population [50]. For six patients taking fluoxetine, the steady-state serum concentration was numerically higher but not significantly different compared with six

participants with normal renal function [37].

Effectiveness and safety

We identified only three RCTs of antidepressant medications (**Figure 4.2**).

One trial is still ongoing (CAST-trial-NCT00946998) and aiming to include 200 participants to evaluate sertraline in a 12-week placebo-controlled randomized trial in patients with CKD3-5 who are diagnosed with major depressive disorder.

The two trials that have been finalized were both conducted in individuals on haemodialysis [24, 25], and required a diagnosis based on a clinical interview using criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the gold standard for psychiatric diagnosis [13].

In the first trial, escitalopram was compared with placebo in 62 patients, but the report was only published as an abstract [25]. The investigators suggested an improvement in depression scores but provided no end-point data. Participants had no serious adverse events. Methodology was insufficiently detailed to allow a clear judgement of the risk of bias. We tried to contact the authors for additional information but did not receive a response. A second study of fluoxetine versus placebo, provided adequate outcome data, but included only 14 patients [24]. On average, after 8 weeks, patients treated with fluoxetine had a 10-point reduction in depression severity on the 63-point Beck Depression Inventory (BDI) scale and a 9-point reduction on the 53-point Hamilton Depression Scale (HAM-D). The results were similar for patients treated with placebo. Adherence was not measured. The number of adverse events was numerically higher in those receiving fluoxetine (34 events

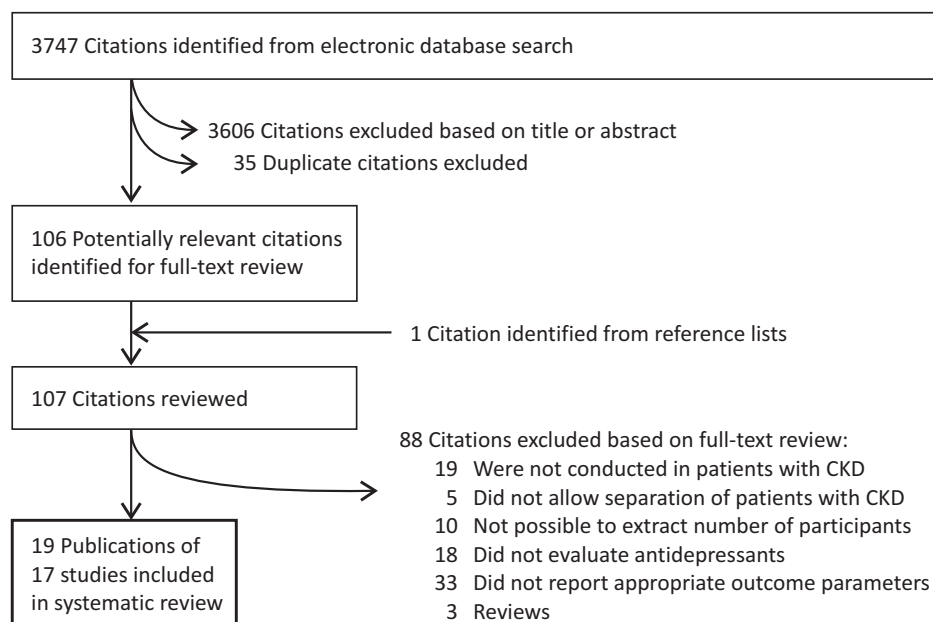


Figure 4.2. Selection process for inclusion of studies in review of efficacy and safety.

in six patients) than in those receiving placebo (22 events in seven patients). Hypotension was reported in four patients in the fluoxetine group versus one in the placebo group. The severity of these events was not specified. Overall, we judged the risk of bias to be low, with adequate sequence generation, allocation concealment, blinding of all participant health-carers, outcome assessors and data analysts, complete reporting of all outcomes and addressing missing data.

We identified nine non-randomized uncontrolled trials, including 7–44 participants each [2–10]. In six studies, patients had to meet the criteria for major depressive disorder as outlined in the DSM-III [2, 4], or DSM-IV clinical psychiatric interview [5, 7, 9, 10, 65, 66]. The three others used various screening tools with a chosen cut-off as inclusion criterion [3, 6, 8]. One evaluated the effects of a tricyclic antidepressant [4], whereas the eight others investigated one of the selective serotonin reuptake inhibitors. In three studies, response by the end of the 4–8-week trial, as defined by a HAM-D score <18 or a reduction of 50% from baseline, varied between 39 and 80% [3, 4, 6]. After 8–12 weeks, depression severity decreased 7–9 points on the BDI scale in four studies [5, 8, 9, 10], and 2–12 points on the HAM-D scale after 8 weeks in two other studies [2, 7]. There were no data on hospitalization rate, all-cause mortality, suicide or suicide attempts and withdrawal from dialysis or for adherence to treatment for CKD.

Two groups investigated the effect of antidepressant treatment on nutritional parameters [6, 7]. In an uncontrolled trial with paroxetine [7], a significant increase in three measures of protein intake was observed. Plasma concentrations of albumin on average increased from 37.3 to 38.7 g/L and those of blood urea nitrogen from 24.3 to 30.2 mmol/L. Normalized protein catabolic rate as a marker of protein intake, significantly increased from 1.04 to 1.17 g/kg/day [7]. The clinical relevance of this outcome might be questioned, given that both values are above the suggested lower limit for malnutrition in dialysis patients of 1 g/kg/day [67]. Conversely, in a non-randomized uncontrolled study conducted in 39 patients on haemodialysis, Lee et al. [6] found no evidence that fluoxetine significantly changed body weight, fat-free mass or arm-muscle index. Adverse events were reported in five trials. The percentage of people suffering from side-effects in these trials varied between 9 and 100%. Complaints were mainly minor and included dizziness, nausea, headache, sedation and somnolence. However, in up to 28% of those suffering side-effects, these caused the patient to discontinue treatment [2–4, 7, 65]. In the one study with a tricyclic agent [4], the investigators stated all patients reported side-effects, most frequently dizziness and dry mouth. However, there was no report of cardiotoxicity and most complaints caused only minor discomfort.

We did identify three retrospective case-reports of serious adverse events associated with the use of a tricyclic compound in patients with severe CKD [68–70]. These included a cardiac arrest associated with the use of maprotiline [68], after exclusion of electrolyte disorders, a case of severe hyperventilation attributed to nortriptyline [70], after exclusion of organic causes of hyperventilation and the development of malignant neuroleptic syndrome in a patient started on amoxapine [69].

We also identified one case report of repeated deep venous thrombosis and subsequent pulmonary embolism in a patient treated with fluoxetine [71], and one case in which a patient developed paranoid ideations while on venlafaxine [72].

Discussion

Summary of main results

For patients with CKD, clearance of various antidepressants is altered. Elimination half-life is prolonged and/or clearance after oral intake markedly reduced for selegiline [50], amitriptylinexide [44], venlafaxine [61], desvenlafaxine [64], milnacipran [52], bupropion [62] and reboxetine [41]. For tianeptine, there is a marked increase in the elimination half-life of its active metabolite [53, 54]. There was large inter-individual variability in every trial and findings are based on single studies, all with methodological shortcomings.

There is no high-quality evidence from randomized trials that suggests antidepressants are more effective than placebo in treating depression in patients with CKD3–5. In addition, there are even only a few reports of prospective observational studies that evaluate the effect of antidepressant drugs in CKD [2–9]. All these studies suggested treatment improved depression after 8–12 weeks but when compared with the only placebo-controlled trial, the magnitude of effect was similar to that of placebo. Side-effects were common, but seemed to be mild in most patients.

Findings in the context of other published literature

A recent Cochrane review on antidepressant drug therapy in the physically ill showed antidepressants to be significantly more effective than placebo (odds ratio 2.33, 95% CI 1.8–3, number needed to treat = 6). At 6–8 weeks, there were more dropouts among patients treated with antidepressants than among patients treated with placebo (number needed to harm = 19) [23].

Of the common side-effects of antidepressant medications, dry mouth and sexual dysfunction were more frequently reported by patients treated with antidepressants.

There was no significant difference in response or adverse effects between tricyclic antidepressants or selective serotonin re-uptake inhibitors. Unfortunately, this meta-analysis included only one trial conducted in patients with CKD.

Strengths and limitations of this study

To our knowledge, this summary of the pharmacokinetics of antidepressants in CKD is the most extensive of its kind at present. It was based on six standard reference works in pharmacology and supplemented with original data from 41 primary studies. We identified these trials by systematically searching seven electronic databases and the reference lists of every obtained publication. However, for most compounds, parameter estimates were still based on single studies with few study subjects and, for all of the studies, we identified

methodological flaws.

Given our knowledge of the recent Cochrane review [23] and our expectation of sparse controlled trial data, we decided to include data from uncontrolled trials to help inform practice.

All published non-controlled trials found a benefit for the antidepressant under investigation, yet effect estimates were similar for the placebo effect found by Blumenfeld et al. in their RCT [24]. Indeed, in depression, on average one-third of participants in clinical trials respond to placebo, making the estimation of any effect size without a placebo control arm problematic. In addition, as on average 21% discontinued the treatment, failure to include outcomes for these patients in the analysis, may have caused the effect size to be overly optimistic. Finally, selective outcome reporting and publication bias might have caused only positive results to have been published [30].

Diagnosis of major depression in patients with CKD is challenging since symptoms of uraemia might mimic those of clinical depression. Clearly, outcomes of interventional trials could be misleading if diagnostic tools fail to distinguish between uraemia and depressive symptoms. Both the randomized trials and six of the nine non-randomized studies required a diagnosis based on a clinical interview using DSM-III or -IV criteria, considered the gold standard to make the diagnosis of depression. Turk et al. used the BDI with a validated cut-off of 15 [72], the other two used screening tools with cut-offs, that had been less validated in patients with CKD.

The available study data point towards a different time lag needed for improvement after antidepressant therapy initiation for patients with CKD (up to 12 weeks) in comparison with the general population (3–6 weeks). Possibly, this is explained by inadequate dosing, drug availability or receptor-drug processing, non-adherence to treatment or somatic influences on treatment success, all of which is subject to further research.

For the present systematic review, studies were selected and data extracted by one person only. Although the findings were carefully checked, failing to include independent study selection and data extraction by a second author increases the risk of errors made in handling of the data.

Last but not least, the recommendations were generated by the authors, nephrologists with expertise in epidemiology. The omission of a multidisciplinary team, including psychiatrists, general practitioners, renal nurses and patients may have caused the statements to insufficiently reflect the views of important stakeholders.

Implications for further research

High-quality efficacy and safety data on the use of antidepressants in advanced CKD are lacking and a well-designed RCT to clarify the balance between benefits and harms is long overdue. We know of only one ongoing randomized trial, comparing sertraline to placebo with a 12-week follow-up, aiming to include 200 patients. Longer follow-up would be needed to demonstrate a sustained benefit of pharmacologic treatment and evaluate

whether hard end-points such as hospitalization and mortality are affected without too many side-effects. Given the lack of adherence and the variability of pharmacokinetic and dynamic effects, larger sample sizes will probably be necessary to reliably show a beneficial treatment effect.

Supplementary data

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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Conflict of interest statement

None declared.

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Diagnosis and treatment of hyponatraemia

*a systematic review of clinical practice
guidelines and consensus statements*

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Abstract

Background. Hyponatraemia is a common electrolyte disorder. Multiple organisations have published guidance documents to assist clinicians in managing hyponatraemia. We aimed to explore scope, content and consistency of these documents.

Methods. We searched MEDLINE, EMBASE, and websites of guideline organisations and professional societies to 09/2014 without language restriction for Clinical Practice Guidelines (defined as any document providing guidance informed by systematic literature review) and Consensus Statements (any other guidance document) developed specifically to guide differential diagnosis or treatment of hyponatraemia. Four reviewers appraised guideline quality using the 23-item AGREE II instrument, which rates reporting of the guidance development process across six domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. Total scores were calculated as standardised averages by domain.

Results. We found ten guidance documents; five clinical practice guidelines and five consensus statements. Overall, quality was mixed: two clinical practice guidelines attained an average score of >50% for all of the domains. Three rated the evidence in a systematic way and two graded strength of the recommendations. All five consensus statements received AGREE scores below 60% for each of the specific domains.

The guidance documents varied widely in scope. All dealt with therapy, and seven included recommendations on diagnosis, using serum osmolality to confirm hypotonic hyponatraemia, and volume status, urinary sodium concentration and urinary osmolality for further classification of the hyponatraemia. They differed however in classification thresholds, what additional tests to consider and when to initiate diagnostic work-up. Eight guidance documents advocated hypertonic NaCl in severely symptomatic, acute onset (<48h) hyponatraemia. In chronic (>48h) or asymptomatic cases, recommended treatments were NaCl 0.9%, fluid restriction and cause-specific therapy for hypovolaemic, euvolaemic and hypervolaemic hyponatraemia respectively. Eight guidance documents recommended limits for speed of increase of sodium concentration, but these varied between 8 and 12 mmol/L per 24h. Inconsistencies also existed in the recommended dose of NaCl, its initial infusion speed, and which second line interventions to consider.

Conclusions. Current guidance documents on the assessment and treatment of hyponatraemia vary in methodological rigour and recommendations are not always consistent.

Background

Hyponatraemia is the most common electrolyte disorder in clinical medicine. It represents an excess of water relative to total body solute [1]. Hyponatraemia usually results from the intake and subsequent retention of electrolyte-free water in response to true hypovolaemia due to gastro-intestinal solute loss or malnutrition; decreased effective circulating volume due to heart failure or liver cirrhosis; or non-osmotic vasopressin activity due to malignancies, infections, medications, pain or stress [2]. When defined as a serum sodium concentration below 135 mmol/L, hyponatraemia occurs in up to 8% of the general population and in up to 60% of hospitalised patients [2, 3]. Acute profound hyponatraemia can cause brain oedema, but also chronic mild hyponatraemia is associated with poor health outcomes. Even when comorbid conditions are taken into account, people with a mildly decreased serum sodium concentration have a 30% higher risk of death and are hospitalised 14% longer relative to those without hyponatraemia [2, 4].

Despite the frequency and severity of some of the associated complications, research suggests hyponatraemia is often neglected by clinicians [5]. If acquired in hospital, it may take days before the electrolyte disorder is investigated, potentially allowing a further decrease in serum sodium concentration and exposing patients to the dangers of profound hyponatraemia. When efforts are made to explore the underlying cause, clinicians use widely different strategies for differential diagnosis, testing is often inadequate and misclassification of the hyponatraemia frequently occurs [6, 7].

Hyponatraemia may be managed clinically by different specialists, such as endocrinologists, nephrologists, geriatricians or intensivists, and accordingly, management strategies often vary [5]. Although probably related to variation in awareness, differences in expert opinion on whom and how to treat only add to the confusion over optimal management. For instance, although experts agree that acute symptomatic hyponatraemia should be treated with hypertonic saline, optimal concentrations and methods for determining initial infusion speeds are debated [1]. In addition, the risk of osmotic demyelination syndrome after rapid correction of hyponatraemia has fuelled intense debate among experts on whether complications of untreated hyponatraemia or complications of treatment pose the greatest risk [8]. As different specialist physicians deal with hyponatraemia, consultation of different information and guidance sources may add to the variability in treatment, seen in clinical practice today.

Clinical practice guidelines and consensus statements provide recommendations to help evidence based practice, by suggesting the most appropriate diagnostic tests and the most appropriate treatments. Over the years, multiple organisations have developed recommendations to assist clinicians in the management of hyponatraemia. To be reliable, these recommendations must be based on a systematic review of the evidence, and have a transparent and multidisciplinary development process [9]. Inconsistencies between recommendations may arise from failing to meet development standards and can only add to unwarranted variability in management. In this study, we aimed to explore the scope,

content and consistency of the existing guidance documents on the diagnosis and management of hyponatraemia in adults and children.

Methods

Criteria for selection of studies

We included evidence-based clinical practice guidelines and consensus statements on the diagnosis and treatment of hyponatraemia. We defined **clinical practice guidelines** as statements that included recommendations intended to optimize patient care informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [9]. We defined consensus statements as documents containing clinically relevant suggestions or recommendations based on the collective opinion of an expert panel [9]. We included all publications independent of language. We excluded guidelines related to the prevention of hyponatraemia. We excluded guidelines relevant to conditions associated with hyponatraemia if they were not specifically designed to address hyponatraemia. Hence, we excluded guidelines targeting treatment of heart failure, cirrhosis and cancer unless they were developed with a focus on hyponatraemia as a complication. Finally, we also excluded draft unpublished guidelines, conference or discussion papers, personal opinions and obsolete guidelines replaced by updated recommendations from the same organisation.

Search methods for guidelines and consensus statements

We searched MEDLINE (1946 to September Week 1, 2014) and EMBASE (1980 to September 2014), combining vocabulary terms and text words for hyponatraemia with terms related to clinical practice guidelines and consensus statements. We also searched guideline databases and websites of organisations, as well as of selected professional specialist societies in Nephrology, Endocrinology and Intensive Care Medicine. A list of the databases and websites along with the full search strategies are outlined in Supplement 1. EN and JV independently screened the titles and abstracts and discarded those that did not meet the inclusion criteria. Full texts for potentially relevant guidelines or consensus statements were retrieved and examined for eligibility. Both the initial screening and subsequent full-paper assessment stage were completed using Early Review Organizing Software (EROS) [10].

Data collection process and data items

We developed a draft data extraction form, which was piloted, and modified as necessary. The extracted data included document characteristics (e.g. year of publication, country/region, development team, funding organisation), recommendations related to the diagnosis and assessment of hyponatraemia, and recommendations related to the treatment of hyponatraemia. EN and JV extracted all data using the standardised data extraction form (Supplement 2) and resolved discrepancies by consensus.

Appraisal of guidelines and consensus statements

Four reviewers independently assessed methodological quality using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument [11]. AGREE II is an internationally validated, rigorously developed 23-item tool used to evaluate six domains of guideline development: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence [12] (Supplement 3). The AGREE tool has also been used to assess consensus statements [13, 14]. The reviewers rated each item on a Likert scale from 1 ('Strongly Disagree') to 7 ('Strongly Agree'). We calculated a total score for each domain by summing up all the scores of the individual items in a domain for each reviewer and then standardizing this total as a percentage of the maximum possible score for that domain, calculated as follows [12]:

$$\frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}} \times 100\%$$

The minimum possible score for each domain equalled the number of questions multiplied by the number of reviewers, multiplied by 1 (strongly disagree). The maximum score for a domain equalled the number of questions multiplied by the number of reviewers, multiplied by 7 (strongly agree). To ensure standardisation of each reviewer's approach, all completed the online training tutorial (<http://www.agreetrust.org/>) before starting the project.

In a consensus meeting among the reviewers, we discussed every item for which scores differed by more than one point (e.g. 1 versus 3) on the original seven-point scale. Reviewers in turn explained the rationale for their score and had the opportunity to revise their score when they considered this appropriate. We audiotaped the consensus meeting to reliably record the underlying reasons for changing scores.

Synthesis of guideline recommendations

We conducted a textual descriptive synthesis to analyse the scope, content and consistency of the included recommendations. EN inductively coded the text manually to identify domains covered by the guidelines. These were cross-tabulated with the guidelines and recommendations were inserted into the corresponding cell. For each domain, we compared guideline recommendations to identify similarities and discrepancies. Consistent with the scope of this review, we only tabulated the information on diagnosis and treatment of hyponatraemia.

Results

Search results

We identified 1402 citations, of which we excluded 1367 after screening titles and abstracts, because they did not meet our eligibility criteria (**Figure 5.1**). We assessed the full

text of the remaining 39 citations and excluded 29 because they were not related to the diagnosis or treatment of hyponatraemia, were not clinical practice guidelines or consensus statements or were guidelines replaced by an updated version (Supplement 4). Ultimately, we included five clinical practice guidelines [15-19] and five consensus statements [20-24]. Six of these documents were retrieved through searching the medical databases [17-19, 22-24], the other four through the search of guideline databases and professional society websites [15, 16, 20, 21].

Table 5.1 shows the general characteristics of the included clinical practice guidelines and consensus statements. Eight national or regional organisations from the Netherlands [15], United Kingdom [16], Northern Ireland [21], Spain [22, 24], United States [17, 18] and Australia [20] and two international groups [19, 23] published these guidance documents between 2004 and 2014. One document specifically covered children [20], the others primarily targeted adults. Six groups reported undertaking a systematic review and appraisal of the evidence [15-19, 23]. Only three were explicit about the level of evidence that underpinned their recommendations [15, 17, 19], and only two graded the strength of the guidance recommendations themselves [17, 19]. Five guidance documents covered hyponatraemia broadly; one specifically covered it in the setting of primary care, one in liver cirrhosis, one in neurosurgery and one in exercise-associated hyponatraemia. Three includ-

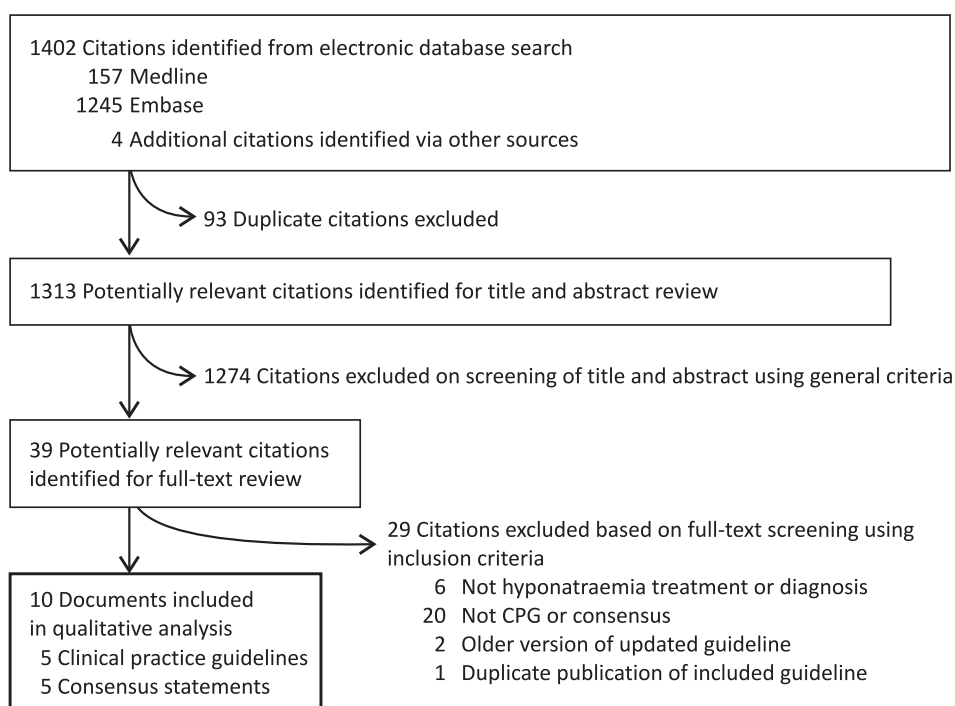


Figure 5.1. Flow diagram of the identification process for clinical practice guidelines and consensus statements on hyponatraemia.

Table 5.1. *Characteristics of included guidelines and consensus statements.*

Devel- oper	Year	Country	Funding source	Target population	Target Users	Guideline writers	Guideline Review	Guideline Update	Methods Sup- port	Evidence Base
Europe										
NIV	2012	Nether- lands	Govern- ment funding	Adults with hyponatraemia	Clinicians, Internists	Multidisciplinary Internists, Epidemiologist	Dutch Associa- tion of Internists (NIV), Expert Peer Review	In case of break- through changes in diagnosis or treatment	PROVA – com- pany specialized in Evidence Based Guideline Development	Systematic Literature Review
NHS	2011	UK	NS	Adults with hyponatraemia in primary care	Primary care professionals within NHS	NS	NS	Planned in 2015	NS	Systematic Literature Review
GAIN*	2010	Northern Ireland	Govern- ment funding	Adults with hyponatraemia	NS	Multidisciplinary Anaesthetists, Clinical Chemist, Nephrologist	NS	3 years	NS	NS
AEFH*	2003- 2004	Spain	NS	Patients with cirrhosis	NS	Gastro-enterologists	NS	NS	NS	NS
EHN*	2013	Spain	NS	Hospitalised patients with SIADH	NS	Multidisciplinary Endocrinologists, Nephrologists, Internists, Hospital pharmacist	NS	NS	NS	Consensus statements
ERBP/ ESE/ ESICM	2014	Europe	Unrestrict- ed grant from par- ticipating societies	Adults with hyponatraemia	Healthcare professionals dealing with hyponatraemia	Multidisciplinary Nephrologists, Endocrinol- ogists, General internists, Critical care physicians	External review by KHA-CARI, ESA and mem- bers ERA-EDTA	5 years or earlier in case of new evidence requir- ing changes	ERBP methods support team	Systematic Literature Review
Devel- oper	Year	Country	Funding source	Target population	Target Users	Guideline writers	Guideline Review	Guideline Update	Methods Sup- port	Evidence Base

Table 5.1. Characteristics of included guidelines and consensus statements. (continued)

North-America										
UF	2008-2009	USA	NS	Neurosurgery patients with hyponatraemia	NS	Multidisciplinary Neurosurgeons, Nurse practitioners, Nephrologists, Critical care physician, Endocrinologist, Pharmacist, Nurses	NS	NS	NS	Systematic Literature Review
HEP	2013	USA	Funding Unrestricted educational grant from pharmaceutical company	Patients with hyponatraemia	NS	Endocrinologist, Nephrologists	NS	NS	NS	Systematic Literature Review
Australia										
RCHM*	2012	Australia	NS	Children	NS	NS	External review within the hospital where appropriate*	12-24 months	NS	NS
International										
EAH-ICD*	2007	USA, Canada, UK, Switzerland, Canada, South Africa, New Zealand, Australia	No commercial sponsorship*	People with exercise-associated hyponatraemia	Medical personnel, athletes, greater public	Multidisciplinary Endocrinologist, Epidemiologist, Nephrologists, Emergency Medicine Physician, general Practitioner, Internist, Sports Physicians, Exercise Physiologists	NS	NS	NS	Systematic Literature Review

NIV – Nederlandse Internisten Vereniging[15]; NHS – National Health Service[16]; GAIN – Guidelines and Audit Implementation Network[21]; AEEH – La Asociación Española para el Estudio del Hígado[22]; ERBP – European Renal Best Practice, ESE – European Society of Endocrinology, ESICM – European Society of Intensive Care Medicine [REF]; UF – University of Florida[17]; HEP – Hyponatremia Expert Panel[18]; RCH Melbourne – the Royal Children's Hospital Melbourne[20]; EAH-ICD – International Exercise-Associated Hyponatremia Consensus Development Conference[29]; *Classified as consensus statement

ed treatment only [22-24], the seven others covered diagnosis as well [15-21]. Two groups reported funding by a governmental institution [15, 21], one by the professional societies they represented [19]; the others did not report their funding sources [16-18, 20, 22-24].

Appraisal of guidelines and consensus statements

Figure 5.2 shows the standardised domain scores for each guideline for each of the six quality domains assessed with the Appraisal of Guidelines for Research and Education (AGREE II) tool (See Supplement 5 for mean individual scores per item across reviewers). The overall quality of reporting of the guideline development process as assessed by AGREE varied widely both between guidance documents across domains and within guidance documents between domains. Overall, guideline developers reported the details of the guideline development process only to a limited extent. Most had average scores below 50% in four to six of the six AGREE II domains [16, 18, 20-24], only two received an average >50% on all six [15, 19].

Guidelines received the highest scores for scope and purpose (median 62%; range 28% to 92%) and clarity of presentation (median 47%; range 27% to 75%) and lowest scores for applicability (median 19%; range 10% to 68%) and editorial independence (median 19%; range 2% to 79%).

Initial appraisal results differed more than one point on the Likert scale between two or more reviewers for 143/230 items (62%). The majority of discrepancies were found in the domain 'Clarity of Presentation', with 90% of items differing more than one point. Group discussion resulted in 287/920 (31%) of individual entries being changed. Finally, no scores differed more than two points and for 82% of items, scores were the same or within one point of each other. Major reasons for changing an entry were a change of own opinion after clarification of the opinion of other reviewers during the group discussion (180/920 entries; 20% entries); aiming for consistency between entries given same available data (39/920; 4%); re-evaluation of the score in light of a noted comment during the appraisal process (30/920; 3%); correction for available data that were overlooked during the initial appraisal (22/920; 2%); misinterpretation of the question during the initial appraisal (6/920; 0.7%); adjusting for arbitrary scoring of items that were felt to be inapplicable for some reason (3/920; 0.3%); adjusting for inconsistent approach to deal with the assumption that a criterion was fulfilled even if this was not clearly mentioned (4/920; 0.4%); data entry error (3/920, 0.3%). Overall this resulted in 29/60 (48%) of standardised domain scores being downgraded by a maximum of 10% and 10/60 (17%) of standardised domain scores being upgraded with a maximum of 10%; the remaining 35% remained unchanged.

Synthesis of recommendations

The included guidance documents addressed three major themes: diagnosis, treatment and speed of correction.

Approaches to diagnostic strategies for hyponatraemia

Seven guidance documents covered diagnosis and differential diagnosis of hyponatraemia [15-21].

Table 5.2 shows the key recommendations. The key areas addressed included the threshold for initiating diagnostic workup, confirmation and classification of hypotonic hyponatraemia, and identification of the underlying disorder.

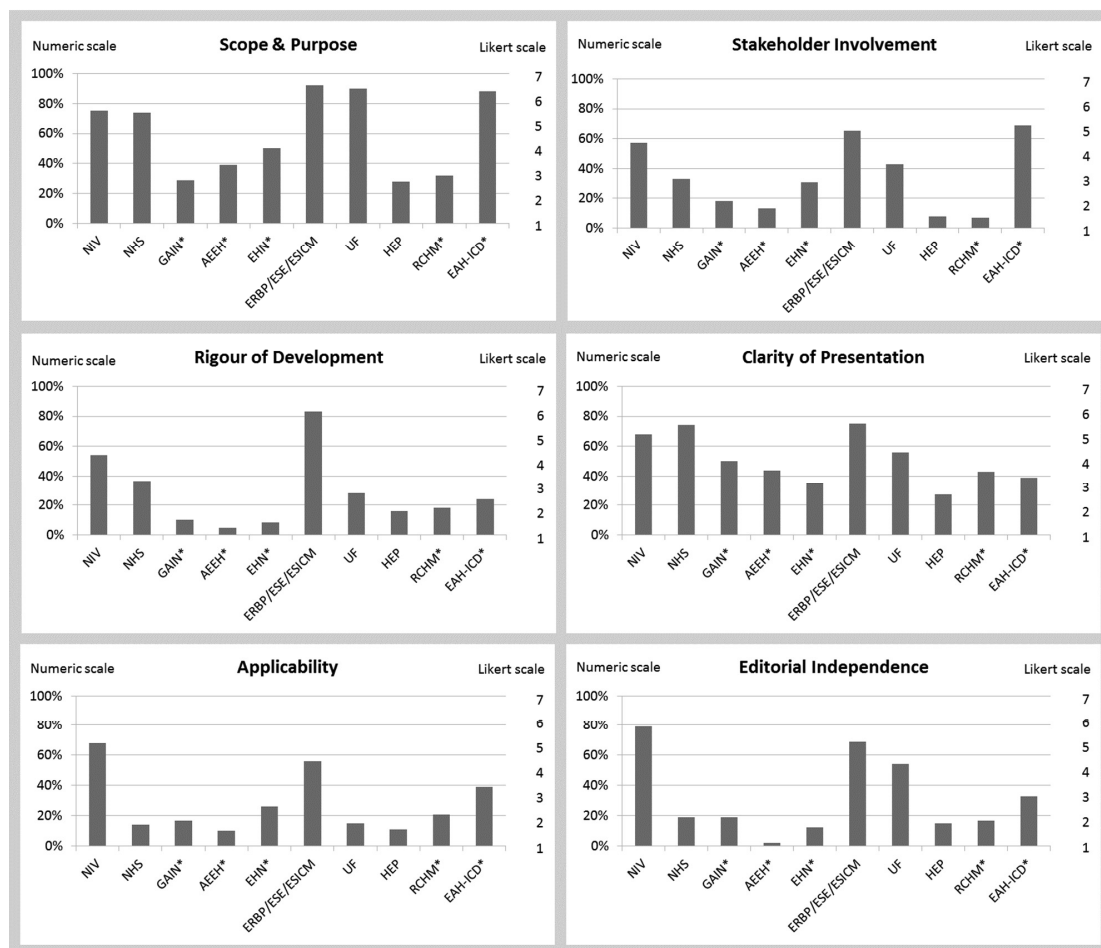


Figure 5.2. Guideline assessment according to the appraisal of guideline for research and evaluation (AGREE II) instrument.

NIV – Nederlandse Internisten Vereniging[15]; NHS – National Health Service[16]; GAIN – Guidelines and Audit Implementation Network[21]; AEEH – La Asociación Española para el Estudio del Hígado[22]; EHN – European Hyponatraemia Network[25]; ERBP – European Renal Best Practice, ESE – European Society of Endocrinology, ESICM – European Society of Intensive Care Medicine [REF]; UF – University of Florida[17]; HEP – Hyponatremia Expert Panel[18]; RCH Melbourne – the Royal Children's Hospital Melbourne[20]; EAH-ICD – International Exercise-Associated Hyponatremia Consensus Development Conference[29]; *Classified as consensus statement.

Note: items were originally scored on a Likert scale of 1 [Strongly Disagree] to 7 [Strongly Agree]. The numerical scores presented for each domain are a summary of individual item scores by each reviewer.

Table 5.2. Summary of recommendations for approaches to diagnosis of hyponatraemia by included guidance documents.

Criteria/Categories	Guideline Organisation/Society				
	NIV[15]	NHS[16]	GAIN[21]	AEHH[22]	EHN [24]
Threshold workup [Na]	< 135 mmol/L	<135 mmol/L	<135 mmol/L	<130 mmol/L	<135 mmol/L
Confirming hypotonic hyponatraemia	Serum osmolality <275 mOsm/kg	Plasma osmolality < 280 mOsm/kg	Serum osmolality <275 mOsm/kg		Plasma osmolality <275 mOsm/kg
How to classify hypotonic hyponatraemia to aid identification of underlying cause					
Volume status/hydration state/ Extracellular fluid status	Clinical evaluation	Physical examination/Clinical signs of dehydration or oedema	Physical examination/Clinical signs of dehydration or oedema		Physical examination/Clinical signs of low circulating volume
Urinary [Na] /Threshold	30 mmol/L	Spot urine: 20-30 mmol/L	15 mmol/L		40 mmol/L
Urinary osmolality/ Threshold	100 mOsm/kg	100 mOsm/kg	100 mOsm/kg		100 mOsm/kg
How to identify the underlying disorder					
History		Medications	Medications		
		Fluid intake	Recently pre-scribed intravenous fluids		
		Nocturnal polyuria	Vomiting /Diarrhoea		
Lab tests					
Serum potassium concentration	+	+			
Serum chloride concentration		+			
Serum urea concentration	+/-	+			
Serum creatinine concentration	+	+			
Serum glucose concentration	+	+	+/-		
Urinary potassium concentration	+				
Renal tests			+		
Liver tests			+		
Urinary protein		+/-			
Thyroid function tests	+/-	+/-	+/-		
Adrenal function tests	+/-	+/-	+/-		
Serum protein electrophoresis		+/-			
Urine protein electrophoresis		+/-			
Fractional sodium excretion	+/-				
Serum uric acid concentration	+/-	+/-			
Fractional uric acid concentration	+/-				
Fractional excretion urea	+/-				
Urinary chloride concentration	+/-				
Molar weight urine	+/-				
Serum bicarbonate concentration					
Haematocrit					

Table 5.2. (continued).

Criteria/Categories	Guideline Organisation/Society				
	ERBP/ESE/ ESICM[19]	UF[17]	HEP[18]	RCHM[20]	EAH- ICD[23]
Threshold workup [Na]	<135 mmol/L	<131 mmol/L	<135 mmol/L	<135 mmol/L	
Confirming hypotonic hyponatraemia	Serum osmolality <275 mOsm/kg	Serum osmolality <285 mOsm/kg	Plasma osmolality <280 mOsm/kg	Serum osmolality threshold not stated	
How to classify hypotonic hyponatraemia to aid identification of underlying cause					
Volume status/hydration state/ Extracellular fluid status	Physical examination/Clinical signs of dehydration or oedema	Physical examination/Laboratory measurements	Physical examination/Laboratory measurements	To assess but method not stated	
Urinary [Na] /Threshold	30 mmol/L	25 mmol/L	Spot urine: 20-30 mmol/L	No threshold stated	
Urinary osmolality/ Threshold	100 mOsm/kg	100 mOsm/kg	100 mOsm/kg	No threshold stated	
How to identify the underlying disorder					
History	Diuretic use				
Lab tests					
Serum potassium concentration				+	
Serum chloride concentration				+	
Serum urea concentration		+/-	+/-	+	
Serum creatinine concentration		+/-	+/-	+	
Serum glucose concentration	+			+	
Urinary potassium concentration		+			
Renal tests					
Liver tests		+/-			
Urinary protein					
Thyroid function tests		+/-			
Adrenal function tests		+/-			
Serum protein electrophoresis					
Urine protein electrophoresis					
Fractional sodium excretion					
Serum uric acid concentration		+	+/-		
Fractional uric acid concentration					
Fractional excretion urea					
Urinary chloride concentration		+	+/-		
Molar weight urine					
Serum bicarbonate concentration		+/-			
Haematocrit		+/-			

[Na]: Serum sodium concentration; + : always; +/- : If clinically indicated/sometimes useful

Guidance documents differed somewhat in their recommended threshold for starting diagnostic assessment. Six recommended starting diagnostic assessment when the serum sodium concentration dropped below 135 mmol/L [16, 18-22] and to confirm hypotonicity through a measured serum or plasma osmolality <275-285 mOsm/kg [15-19, 21]. Two others set lower thresholds of serum sodium concentration <131 mmol/L [17] and <130 mmol/L [22]. Six guidance documents advised classifying hypotonic hyponatraemia into categories of hypovolaemia, euvoemia and hypervolaemia to aid differential diagnosis and guide treatment [15-21]. Most guidance documents recommended a clinical assessment of hydration status and a urinary sodium concentration as well as a urinary osmolality measurement, although specific criteria, thresholds and algorithms differed.

Most guidance documents proposed additional laboratory tests that could be of value to identify the underlying disorder, but they varied substantially in which tests to use in what situation and which reference values to use. Only two explicitly recommended taking a history of drug intake and symptoms as part of the assessment [16, 21]. Four presented an algorithm to guide differential diagnosis [15, 17, 19, 21].

Approaches to treatment for hyponatraemia

Table 5.3 shows the recommendations for the medical management of hyponatraemia. Guidance documents distinguished treatment scenarios based on whether patients had severe symptoms [16-21, 23, 24] or whether the hyponatraemia was acute (48h) or chronic [15]. All but one discussed treatment in the setting of severe symptoms and recommended infusion of hypertonic saline, usually specified as having a concentration of 3% [16, 18-20, 23, 24]. One suggested using a formula to guide the infusion speed of a continuous infusion [15], five others recommended giving a fixed dose [18, 19, 21, 23, 24] or a dose adjusted to body weight [20, 24] with repeated serum sodium concentration measurements to check progression [15, 19-21, 24].

Patients without symptoms of hyponatraemia were assumed to have chronic onset hyponatraemia, and treatment suggestions were mostly dependent on the classification hypovolaemic, euvoaemic, hypervolaemic. Only three guidance documents specifically advised treating the underlying condition [18, 19, 21]. Seven suggested 0.9% saline in hypovolaemia [15-21], with infusion speeds calculated with Adrogue-Madias [21], until restoration of blood pressure [16, 18] or until nasogastric rehydration could start [20].

For euvoaemic asymptomatic hyponatraemia, the majority recommended fluid restriction as the first-line treatment [15-24]. Five guidance documents proposed a number of other interventions as second-line treatments including loop diuretics [15, 17, 19, 24], demeclocycline [15-18], urea [15, 18, 19, 24], vasopressin-receptor antagonists [15, 16, 24] or lithium [17]. One guideline specifically recommended against vasopressin receptor antagonists in case of a serum sodium concentration <125 mmol/L [19].

For hypervolaemic asymptomatic hyponatraemia, seven guidance documents recommended fluid restriction as the first-line treatment [15, 16, 18-22] (Table 5.3). Three guidance documents advocated concomitant salt restriction, without clear dose recommendations

Table 5.3. Summary of recommendations for approaches to treatments for hyponatraemia by included guidance documents.

Criteria/ Categories	Guideline Organisation/Societies									
	NIV [15]	NHS [16]	GAIN [21]	AEEH [22]	EHN [24]	ERBP/ESE/ ESICM [19]	UF [17]	HEP [18]	RCHM [20]	EAH-ICD [23]
Symptoms										
Acute Onset (<i><48h</i>)	NaCl >1% Infusion speed may be guided by Adrogué- Madias	NaCl 3%	NaCl 2.7% 200 mL over 30 min		NaCl 3% 100 mL/10 min up to 3x or infused at 0.5-2 mL/ kg/h	NaCl 3% 150 mL/20 min up to 4x	NaCl >1%	NaCl 3% 100 mL/10 min up to 3x or infused at 0.5-2 mL/kg/h	NaCl 3% 4 mL/kg over 30 min	NaCl 3% 100 mL bolus
Hypovolaemia	NaCl 0.9% until blood pressure re- stored									
Euvolaemia	Fluid restriction Stop offending drugs Stop hypotonic fluids									
Hypervolaemia	Furosemide									
Chronic Onset (<i>>48h</i>)	NaCl >1% Infusion speed calculation may be guided by Adrogué- Madias	NaCl 3%	Only if severe symp- toms NaCl 2.7% 200 mL over 30 min Infusion speed by may be guided Adrogué-Madias		NaCl 3% 100 mL/10 min up to 3x or infused at 0.5-2 mL/ kg/h	NaCl 3% 150 mL/20 min up to 4x	NaCl >1%	NaCl 3% 100 mL/10 min up to 3x or infused at 0.5-2 mL/kg/h		
Hypovolaemia	NaCl 0.9% 1L over 2-4h Infusion speed may be guided by Adrogué-Madias									
Euvolaemia	Fluid restriction Stop offending drugs Stop hypotonic fluids									
Hypervolaemia	Furosemide									

Table 5.3. (continued)

Criteria/ Categories	Guideline Organisation/Societies									
	NIV [15]	NHS [16]	GAIN [21]	AEHH [22]	EHN [24]	ERBP/ESE/ ESICM [19]	UF [17]	HEP [18]	RCHM [20]	EAH-ICD [23]
No Symptoms										
Acute Onset (<48h)	NaCl >1% Infusion speed by Adrogué- Madias		Treat underlying condition			Stop offending fluids and medi- cations Treat underlying condition NaCl 3% 150 mL/20 min			Treat underlying condition	
Chronic Onset (>48h)	Treat underly- ing condition		Treat underlying condition			Stop non-essen- tial fluids Stop offending medications Treat underlying condition		Treat underly- ing condition		
Hypovolaemia	NaCl 0.9%	NaCl 0.9% until blood pressure restored	NaCl 0.9% Infusion speed may be guided by Adrogué-Madias			NaCl 0.9% or bal- anced crystalloid 0.5-1 mL/kg/h	NaCl 0.9%	NaCl 0.9% until blood pressure re- stored	Nasogastric rehydration	
	NaCl tablets							No VPA	NaCl 0.9%	
Euvolaemia	Fluid restriction, Dose depend- ant on serum and urinary electrolytes	Fluid restric- tion, 500-1000 mL/d	Fluid restriction		Fluid restric- tion <500- 1000 mL/d	Fluid restriction	Fluid restric- tion	Fluid restriction 500 mL below average daily urine output	Fluid restric- tion No hypotonic fluids	
	Loop diuretics	No salt restriction	Salt restriction		Salt 5-8g/d			No salt restric- tion		
					Furosemide 20-60 mg/d + oral NaCl	Loop diuretics, low dose + oral NaCl		Diuretics		
	Demeclocycline	Demeclo- cycline			No demeclo- cline	Demeclo- cline		Demeclocycline, 600-1200 mg/d		
	Urea				Urea 30 g/d	Urea, 0.25-0.5 g/ kg/d	Urea	Urea, 15-60 g/d		
	Vasopres- sin receptor antagonist	Vasopressin receptor antagonist			Tolvaptan 15- 60 mg/d	No vasopressin receptor antago- nists				
					No lithium			Lithium		

Table 5.3. (continued)

Criteria/ Categories	Guideline Organisation/Societies									
	NIV [15]	NHS [16]	GAIN [21]	AEEH [22]	EHN [24]	ERBP/ESE/ ESICM [19]	UF [17]	HEP [18]	RCHM [20]	EAH-ICD [23]
Hypervolaemia		Treat underlying condition								
	Fluid restriction, Dose depend- ent on serum and urinary electrolytes	Fluid restric- tion	Fluid restriction	Fluid restric- tion <1000 mL/d		Fluid restriction		Fluid restriction, <insensible losses + urine output	Fluid restric- tion	
	Loop diuretics	Salt restric- tion	Salt restriction	No NaCl >0.9%				Salt restriction		
		Demeclo- cycline		Stop diuretics		No demeclo- cycline		Possibly vaso- pressin receptor antagonist		
		Vasopressin receptor antagonist				No vasopressin receptor antago- nist				

[16, 18, 21], and one to avoid hypotonic infusion solution [20]. Three additionally proposed loop diuretics [15, 16, 18], three others generally stated to treat the underlying disease [16, 19, 21], whereas one advised to consider stopping diuretics [22]. One guideline additionally proposed demeclocycline and two proposed vasopressin receptor antagonists as a second-line treatment for refractory hyponatraemia [16, 18], whereas one guideline specifically recommended against both demeclocycline and vasopressin receptor antagonists [19].

Targets and limits of speed of correction

Table 5.4 shows the key recommendations. The key areas include targets and limits for increase in serum sodium concentration.

Seven guidance documents provided *targets* or aims for the increase in serum sodium concentration in case of symptomatic and/or acute hyponatraemia [15, 16, 18-21, 24]. Seven guidance documents provided *limits* for the increase in serum sodium concentration that should not be surpassed [15-21, 24]. Five did so independent of symptoms [15, 17, 19, 21, 24]. Limits usually varied between 8 to 12 mmol/L during the first 24 hours [15-21, 24] and 18 mmol/L during the first 48 hours [15, 16, 18, 19, 24], irrespective of whether hyponatraemia was acute or chronic [15, 16, 19, 24]. Three guidance documents set a stricter limit of <8 mmol/L during the first 24 hours in case the patient was felt to be high risk for developing osmotic demyelination syndrome [15, 18, 24]. Four discussed what to do in case of overcorrection, i.e. to stop current treatment, and to consider re-lowering serum sodium concentration by starting hypotonic infusion and administering 1-4 µg desmopressin every six to eight hours [15, 18, 19, 24].

Discussion

We found five clinical practice guidelines and five consensus statements covering the diagnostic approach to and treatment of hyponatraemia. Although most used serum osmolality, volume status, urinary sodium and urinary osmolality to guide differential diagnosis, they differed in classification thresholds, what additional tests to consider and when to initiate diagnostic work-up. Most advocated hypertonic NaCl in severely symptomatic, acute onset hyponatraemia and NaCl 0.9%, fluid restriction and cause-specific therapy for hypovolaemic, euvolaemic and hypervolaemic hyponatraemia respectively. However, they somewhat differed in the limits for speed of increase in serum sodium concentration and which specific medications to use. The reasons for offering different recommendations are undoubtedly multifactorial. They may in part be explained by the fact that recommendations were issued by organisations differing in context and scope. It is also very likely that some variability in guidance arose through limitations in the evidence available for guideline developers to base their recommendations on [8]. In the most recent guideline on diagnosis and treatment of hyponatraemia 98% of the graded recommendations were based on very low and low level of evidence, while none were based on a high level of evidence. The lack of high quality evidence may have increased the part opinion had to play in framing the

Table 5.4. Summary of recommendations for targets and limits for speed of correction of hyponatraemia by included guidance documents.

Criteria/Categories Guideline Organisation/Societies											
	NIV [15]	NHS [16]	GAIN [21]	AEHH [22]	EHN [24]	ERBP/ESE/ ESICM [19]	UF [17]	HEP [18]	RCHIM [20]	EAH-ICD [23]	
Targets [Na] Increase											
Symptoms	Independent of symptoms	If symptoms	If symptoms	If symptoms	If symptoms	If symptoms	If symptoms	If symptoms	Until seizures resolve or [Na] >125 mmol/L		
Acute Onset (<48 h)	1-2 mmol/L/h initially	Until [Na] > 120 mmol/L independent of onset	1-2 mmol/L/h first 2-3 h	1-6 mmol/L first 2h	5 mmol/L first h	4-6 mmol/L urgently	Independent of onset				
Chronic Onset (>48 h)		0.5-1 mmol/L/h first 2-3 h	1-6 mmol/L first 2h	5 mmol/L first h	If seizures or coma 4-6 mmol/L urgently, otherwise 4-6 mmol/L per 24 h						
Limits [Na] Increase											
Symptoms	Independent of symptoms	If no symptoms	Independent of symptoms	Independent of symptoms	Independent of symptoms	Independent of symptoms	Independent of symptoms	If no symptoms	Symptom dependent		
Acute Onset (<48 h)	If no risk of ODS ≤10 mmol/L per 24h ≤18 mmol/L per 48h	≤8-12 mmol/L per 24h ≤18 mmol/L per 48h	<12 mmol/L per 24h	≤10 mmol/L per 24h	If no risk of ODS ≤10 mmol/L per 24h ≤18 mmol/L per 48h	≤10 mmol/L first 24h ≤8 mmol/L every 24h thereafter	≤10 mmol/L per 24h	No limits	≤8 mmol/L per 24h after seizures resolve, Independent of onset		
Chronic Onset (>48 h)	If risk of ODS <8 mmol/L per 24h	If risk of ODS <8 mmol/L per 24h	<12 mmol/L per 24h	≤10 mmol/L per 24h	If risk of ODS <8 mmol/L per 24h	≤10 mmol/L first 24h ≤8 mmol/L every 24h thereafter	≤10 mmol/L per 24h	<8-10-12 mmol/L per 24h	<18 mmol/L per 48 h		

[Na] – Serum sodium concentration

recommendations. In addition, the evidence that was available may have been interpreted differently dependent on the importance for decision making given to certain outcomes (e.g. serum sodium concentration). Finally, differences in personal experience due to differing availability of medications may partly explain possible differences in perception of uncertainties around drug safety.

However, it is also possible that discrepancies between guidance documents may in part be explained by differences in underlying methods of development. Quality, as assessed by AGREE II was suboptimal at best, with only two documents obtaining a score > 50% for each of the six quality domains [15, 19]. The findings suggest that several aspects related to methodological rigour of development, stakeholder involvement, applicability and editorial independence could be improved, possibly improving consistency in provided guidance. This is in line with the findings of a recent overview of 42 appraisal studies including a total of 626 clinical practice guidelines across several clinical disciplines [25].

For guidelines to be trustworthy, they must be 1) founded on high quality systematic reviews, 2) include the relevant stakeholders and 3) be applicable in clinical practice [9].

Only half of the guidance groups stated they had conducted a systematic review of the evidence. Save one, the reviews would not have met the Institute of Medicine's criteria for reporting high-quality systematic reviews [19, 26], because key methods for finding and assessing individual studies as well as synthesizing the body of evidence were not described. Conducting high-quality systematic reviews requires specific methodological expertise and support which may not be available to most groups [26]. One solution might be to harmonise effort across organisations, thus focussing resources, allowing higher quality reviews, reducing duplication and possibly inconsistency between guidelines.

Six groups included healthcare professionals from different specialties [15, 17, 19, 21, 23, 24]. Multidisciplinary contribution serves to broaden the approach to healthcare problems, increase the completeness of evidence finding strategies and help to identify hurdles to implementation. When reflecting on approaches to hyponatraemia, bringing together several disciplines mirrors the clinical reality of multiple specialty areas dealing with the same problem but looking at it from a different angle. Only one of the development groups reported considering patients' views and experiences, but even then did so to a limited extent [19]. Decisions on clinical care should factor in patient values and preferences. Interventions for chronic hyponatraemia, such as fluid restriction, may affect quality of life and patient preference should influence the ultimate recommendations.

Low scores for applicability mostly reflect the absence of describing barriers to guideline implementation and failure to provide tools for putting the recommendations into practice. In part, guidelines are designed to deal with the challenges of increasing knowledge and time-pressure. They are designed to help make decisions at the point of care. However, being often lengthy publications without layered presentation of information, the majority of the guidance documents may not be likely to reach their target audience or stimulate implementation. Four guidance documents provided algorithms for diagnosis or treatment [15, 17, 19, 24]. Although these are likely to increase the utility of a guideline, it is unclear

to what extent they truly improve implementation of the recommendations. How to best communicate evidence-based recommendations to the relevant stakeholders is a recent but active area of research lead by the DECIDE consortium [27]. With results of their research expected, guideline developers will have additional targets for improving the applicability in the future.

To our knowledge, this is the first attempt to systematically synthesize and appraise clinical guidelines on the diagnosis and treatment of hyponatraemia. We conducted a comprehensive search and searched an additional 337 websites of specialist societies and guideline organisations. We used AGREE II, a validated and reliable instrument, and an adequate number of reviewers to individually appraise the guidance documents [28]. On top of the individual appraisals, we included an attempt to resolve major discrepancies and increase consistency by introducing an audiotaped group consensus meeting. During this meeting, reviewers could explain and motivate their scores and adapt them if they wanted to. This mostly resulted only in modest downgrading of domain scores by 1% to 10%. Most of the changes happened because reviewers felt they had scored inconsistently for a same rationale, or because they missed information during the initial appraisal that was in fact available in the document. Although the scores did not change substantially, the group felt the discussion further highlighted the qualitative differences between the guidance documents. In addition, even the reviewers with large deviations from the mean in their initial scores felt they agreed with the conclusion. It means that final average scores were truly a product of consensus rather than a mathematical calculation, as proposed in the original AGREE protocol. We believe that a consensus meeting is valuable in any guideline appraisal process, and particularly useful if reviewer groups have the intention to select a guideline for local use.

This study has its limitations. We based our assessment on what guideline organisations actually reported. Reporting by guideline developers may not wholly reflect what occurred in practice with respect to the AGREE criteria, and we did not seek additional clarification. However, contacting guideline developers is not standard practice when using AGREE as the instrument specifically aims to provide a framework for assessing the quality of reporting of recommendations. We aimed to summarize the existing recommendations on diagnosis and treatment of hyponatraemia as formulated by other guideline development groups and to evaluate the quality of the guideline development process. We did not aim to summarize or critically appraise the evidence base itself. Consequently, it is difficult to assess to what extent differences between guidance documents stem from differences in development procedures rather than important limitations in the evidence base that underpin individual recommendations. Secondly, the purpose of using the AGREE instrument was not to accuse guideline development groups of being biased, but rather to highlight both strengths and weaknesses of existing guidance to suggest on how we could make improvements in the future.

Calculation of summary scores for each domain across reviewers required summing up all the scores of the individual items in a domain for each reviewer and then standardizing this total as a percentage of the maximum possible score for that domain. In doing so, the

originally semi-qualitative Likert scale was converted to a quantitative score. This may have introduced numeric differences between the guidance documents that were beyond the discriminatory ability of the tool and possibly negligible in practice. Finally, we acknowledge that four of the authors of this paper also authored one of the guidelines included in this review. Although we aimed to judge all guidance documents fairly against the criteria outlined by the AGREE instrument, we cannot rule out that a subconscious intellectual competing interest unduly influenced the scoring.

Conclusions

Current guidelines on the assessment and treatment of hyponatraemia often fail to meet methodological criteria for development and reporting as described by AGREE II. Despite many similarities, recommendations are sometimes inconsistent, but to what extent this is attributable to the underlying development process remains unclear.

Competing interests

Evi Nagler is a member of the Methods Support Team of European Renal Best Practice (ERBP). She is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatraemia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review. Jill Vanmassenhove has no relevant disclosures. Sabine van der Veer is a member of the Methods Support Team of European Renal Best Practice (ERBP). She is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatraemia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review. Ionut Nistor is a member of the Methods Support Team of ERBP. Wim Van Biesen is the Chair of ERBP, he is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatraemia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review. Angela Webster has no relevant disclosures. Raymond Vanholder is member of ERBP, he is also one of the authors of the Clinical Practice Guideline on the diagnosis and treatment of hyponatraemia, developed in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine and one of the guidelines included in the current review.

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**Interventions for chronic
non-hypovolaemic
hypotonic hyponatraemia**
*a systematic review of
randomised controlled trials*

Chapter 6: Contents

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Abstract

Background. Chronic (present >48 hours) non-hypovolaemic hypotonic hyponatraemia occurs frequently and is associated with increased mortality. Whether correction of the hyponatraemia by itself can improve outcomes is less certain.

Objectives. We aimed to evaluate the benefits (reductions in all-cause mortality, health-related quality of life and specifically symptoms attributed to hyponatraemia) and harms (osmotic demyelination syndrome, rapid increase in serum sodium concentration, treatment-specific side-effects) of any intervention versus placebo, no treatment, standard care, or another active intervention in children and adults with chronic non-hypovolaemic hypotonic hyponatraemia.

Search methods. We searched the Cochrane Renal Group's Specialised Register to 22 April 2015 through contact with the Trials Search Co-ordinator using search terms relevant to this review.

Selection criteria. We included randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of any intervention with placebo, no treatment, standard care, or any other intervention in patients with chronic non-hypovolaemic hypotonic hyponatraemia. We also included subgroups with hyponatraemia from studies with broader inclusion criteria (e.g. people with chronic heart failure or people with cirrhosis with or without hyponatraemia), provided we could obtain outcomes for participants with hyponatraemia from the report or the study authors.

Data collection and analysis. Two authors independently extracted data and assessed risk of bias. We expressed treatment effects as mean difference (MD) for continuous outcomes (health-related quality of life, length of hospital stay, change from baseline in serum sodium concentration, cognitive function), and relative risk (RR) for dichotomous outcomes (death, response and rapid increase in serum sodium concentration, hypernatraemia, polyuria, hypotension, acute kidney injury, liver function abnormalities) together with 95% confidence intervals (CI).

Main results. 28 studies (3189 participants) compared a vasopressin receptor antagonist versus placebo, usual care, no treatment or fluid restriction. In adults with chronic, non-hypovolaemic hypotonic hyponatraemia, vasopressin receptor antagonists modestly increased the serum sodium concentration (MD 4.17, 95% CI 3.18 to 5.16) and slightly reduces hospital stay (MD -1.63 days, 95% CI -2.96 to -0.30), but had unclear effects on all-cause mortality (RR 1.11, 95% CI 0.92 to 1.33), was associated with an increased risk of rapid serum sodium correction (RR 1.67, 95% CI 1.16 to 2.40) and commonly caused side-effects such as thirst (OR 2.77, 95% CI 1.80 to 4.27) and polyuria (RR 4.69, 95% CI 1.59 to 13.85). Effects were generally consistent across the different agents, suggesting class effect. The evidence on patient-important outcomes such as health-related quality of life, cognitive and general functional

status was limited and generally showed no important beneficial treatment effect. Overall, based on GRADE criteria, evidence for vasopressin receptor antagonists in people with hyponatraemia (mortality, change and rapid increase in serum sodium concentration) was of low quality and suggested that additional studies may change our confidence in the estimates of effect or our confidence in these results.

Data for other interventions such as fluid restriction, urea, mannitol, loop diuretics, corticosteroids, demeclocycline, lithium and phenytoin were largely absent.

Authors' conclusions. In people with chronic hyponatraemia, vasopressin receptor antagonists modestly raise serum sodium concentration at the cost of a 3% increased risk of it being rapid, and a subsequent small but unknown increased risk of osmotic demyelination syndrome. To date there is little evidence from RCTs for a beneficial effect on mortality, quality of life or any other truly important health outcome of these agents or in fact any other treatment for chronic hyponatraemia. It makes any recommendation problematic.

Further studies assessing standard treatments such as fluid restriction or urea against placebo and one-another would inform practice and are warranted given limited evidence that in chronic hyponatraemia aside from affecting the surrogate (increase in serum sodium concentration) any treatment results in improved patient-centred outcomes.

Background

Description of the condition

Hypotonic hyponatraemia is a common condition, occurring in up to 60% of people admitted to hospitals, depending on the definition of hyponatraemia, the types of patients who are studied and the healthcare facility to which these patients are admitted (Upadhyay 2009). Hypotonic hyponatraemia is usually defined as a serum sodium concentration < 135 mmol/L with an osmolality < 285 mOsm/kg (Reynolds 2006). It develops when the body retains an excess of water relative to the amount of sodium. It can be caused by intrinsic kidney disease but usually results from incomplete suppression of vasopressin activity despite decreased tonicity of the plasma. In situations of decreased circulating blood volume, vasopressin release is increased in a physiologic response to maintain haemodynamic homeostasis. This occurs either with true volume depletion or with reduced effective arterial circulating volume, as seen in heart failure, liver cirrhosis or nephrotic syndrome. In the syndrome of inappropriate antidiuretic hormone secretion, the increased release of vasopressin is non-haemodynamic and can have multiple causes including ectopic production of vasopressin by a variety of tumours (Verbalis 2013).

When plasma tonicity is low, water tends to enter the cells and causes them to swell. If blood sodium concentrations drop rapidly (within a 48 hour period), the swelling of brain cells may lead to brain oedema, brain stem herniation and eventually even death. Fortunately, when blood sodium concentrations drop more gradually, brain cells adapt to their hypo-osmolar surroundings and prevent swelling by the transport of solutes from the intracellular to the extracellular compartments. As a consequence, immediate symptoms attributable to chronic hyponatraemia are usually less severe than for acute hyponatraemia (Reynolds 2006). Nevertheless, people with chronic hyponatraemia have reduced attention and less stable gait than those without hyponatraemia (Renneboog 2006). They fall more often and have increased risk of osteoporosis and bone fractures (Arampatzis 2013; Hoorn 2011; Kinsella 2010; Renneboog 2006; Verbalis 2010). Finally, they stay in hospital longer and have an increased risk of death, even when sodium concentrations are only mildly decreased and underlying or comorbid conditions are adjusted for (Wald 2010).

Description of the intervention

It is accepted that acute hypotonic hyponatraemia requires an immediate increase in serum sodium concentration to prevent severe neurologic complications (Ellison 2007). What to do with chronic hypotonic hyponatraemia is less clear. Firstly, chronic non-hypovolaemic hypotonic hyponatraemia has been treated under the assumption that increasing the sodium concentration improves important health outcomes; that patients live longer, feel better and are hospitalised less frequently. Although several observational studies have indicated an association between hyponatraemia and undesirable outcomes, it is still unclear whether correcting the hyponatraemia improves them (Upadhyay 2009; Wald 2010).

Secondly, once brain cells have adapted to their hypo-osmolar environment, they become vulnerable to osmotic demyelination in case the environment is restored. Although rare, osmotic demyelination is a devastating neurologic complication that may occur when the myelin sheath around pontine and extrapontine neurons breaks down after rapid rises in serum sodium concentration. It very rarely does if the increases stay below 8 to 12 mmol/L/24 h and 18 mmol/L/48 h (Adroque 2012; Ellison 2007; Reynolds 2006). Treatment for chronic hypotonic hyponatraemia must balance the uncertain benefit of increasing the sodium concentration against the risk of complications due to overly rapid correction.

How the intervention might work

Whatever the underlying cause, chronic non-hypovolaemic hypotonic hyponatraemia usually results from urine being insufficiently dilute to maintain serum osmolality within the normal range (Adroque 2000). Several treatment strategies can be used to try overcoming this (Adroque 2012; Ellison 2007; Verbalis 2013).

Restriction of fluid intake aims to decrease the amount of free water needing excretion. Urea and mannitol improve electrolyte-free water clearance by increasing urine osmolality and creating osmotic diuresis (Lindner 2012). Loop diuretics, such as furosemide, bumetanide and ethacrynic acid, impair free-water absorption in the collecting duct by reducing the hypertonicity of the renal medulla. Corticosteroids with a mineralocorticoid effect increase renal sodium retention by active reabsorption of sodium in the principal cells of the cortical collecting tubule. Demeclocycline, lithium, phenytoin and vasopressin receptor antagonists act by pharmacologically inhibiting the effect of antidiuretic hormone on the principal cells of the collecting duct, thereby limiting insertion of water channels in the luminal membrane and thus preventing free water reabsorption.

As hyponatraemia with true volume depletion (chronic hypovolaemic hypotonic hyponatraemia) is treated by restoring volume with water and salt, we do not cover it in this review.

Why it is important to do this review

The benefits and harms of treatments for chronic non-hypovolaemic hypotonic hyponatraemia have not been formally evaluated in a systematic review. Two systematic reviews have explored the efficacy and safety of vasopressin receptor antagonists (e.g. conivaptan, lixivaptan, satavaptan, tolvaptan) versus placebo, no treatment or fluid restriction (Jaber 2011; Rozen-Zvi 2010), but to our knowledge there has been no attempt to compare them with any other intervention or to compare any of the other interventions versus placebo or against one another.

Both systematic reviews have found an early increase in serum sodium concentration, but no improvement in outcomes important to patients. Indeed, most randomised controlled trials (RCTs) have evaluated short-term and surrogate outcomes only, making it difficult to adequately assess any expected benefit in the long-term. Since the most recent

systematic review was published, 12 additional RCTs comparing vasopressin receptor antagonists versus control have been completed, increasing the total sample size by at least 50%. Although outcomes are still mostly surrogate and short-term, the largest study was terminated early due to a numeric imbalance in the number of early deaths in the experimental group (FDA 2012). We believe it justifies reanalysis including in-depth investigation of possible heterogeneity at this point.

Objectives

This review aimed to look at the benefits and harms of interventions for chronic non-hypovolaemic hypotonic hyponatraemia when compared with placebo, no treatment or head-to-head.

The review aimed to determine if benefits and harms vary in absolute or relative terms dependent on the specific compound within a drug class, on the dosage used, or the underlying disorder causing the hyponatraemia.

Methods

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at interventions for chronic, non-hypovolaemic hypotonic hyponatraemia.

We also included data for hyponatraemia subgroups within studies with broader inclusion criteria (e.g. people with chronic heart failure or people with cirrhosis with or without hyponatraemia) which report outcomes for participants with hyponatraemia, or where we could obtain these subgroup data from the study authors.

Types of participants

Inclusion criteria

- Adults and children beyond the neonatal period (the interval from birth to 28 days of age)
- Chronic, hypotonic hyponatraemia: presence of hyponatraemia > 48 hours, serum osmolality < 285 mOsm/kg and serum sodium concentration < 135 mmol/L, or as defined by authors); not requiring immediate treatment and due to:
 - decreased effective circulating volume in the setting of heart failure, liver cirrhosis or nephrotic syndrome
 - inappropriate antidiuresis, associated with any underlying condition (includes syndrome of inappropriate antidiuretic hormone secretion and nephrogenic syndrome of inappropriate antidiuresis)

- impaired renal dilutional capacity due to kidney disease.

Sodium concentrations can be measured in any type of blood sample (e.g. serum, plasma, whole blood, venous, arterial, capillary) using any measurement method (e.g. flame emission spectrophotometry, direct or indirect reading potentiometry by an ion-selective electrode) in any setting (e.g. central laboratory, local laboratory, point of care device).

Exclusion criteria

- Children in the neonatal period (the interval from birth to 28 days of age)
- Isotonic or hypertonic hyponatraemia (osmolality ≥ 285 mOsm/kg)
- Hyponatraemia due to true (extracellular) volume depletion, such as from third spacing (type of fluid leakage into interstitial spaces seen in pancreatitis, bowel obstruction, sepsis,...), and gastrointestinal, or renal sodium loss
- Hyponatraemia due to secondary adrenal insufficiency or hypothyroidism
- Hyponatraemia due to primary psychogenic polydipsia
- Patients treated with any form of dialysis or extracorporeal ultrafiltration.

Types of interventions

We included studies of any degree of fluid restriction or any drug treatment that has the aim of increasing the sodium concentration. Any dose or route of administration was permitted, and interventions could be compared with placebo, no treatment, a different dose of the same or different interventions, different administration routes of the same or different interventions, or different combinations of interventions.

Treatments included (but were not limited to):

- vasopressin receptor antagonists (conivaptan, mozavaptan, lixivaptan, satavaptan, tolvaptan)
- fluid restriction
- urea
- mannitol
- loop diuretics (furosemide, bumetanide, ethacrynic acid)
- corticosteroids (hydrocortisone or equivalent, fludrocortisone)
- demeclocycline
- lithium
- phenytoin.

We excluded studies in which any form of dialysis treatment was given to correct serum sodium concentration.

Types of outcome measures

We assessed outcomes up to one week, up to one, two and six months, and up to one and five years.

Primary outcomes

- Death (all-cause mortality)
- Health-related quality of life and specifically symptoms attributed to hyponatraemia by trialists.

Secondary outcomes

- Length of hospital stay
- Serum sodium concentration (mmol/L) at end of treatment or change from beginning to end of treatment
- Response defined as increase of ≥ 5 mmol/L or normalisation of serum sodium concentration (≥ 135 to 145 mmol/L, or as defined by the authors)
- Outcomes related to over-correction of serum sodium concentration
 - Incidence of hypernatraemia (serum sodium concentration > 145 mmol/L, or as defined by the authors)
 - Rapid increase in serum sodium concentration (increase in serum sodium concentration > 8 -12 mmol/L in 24 h or > 18 mmol/L in 48h, or as defined by the authors)
 - Incidence of osmotic demyelination syndrome, previously known as central pontine and extrapontine myelinolysis (diagnosed clinically, by MRI, or post mortem)
- Any treatment-specific side effects as defined by authors
 - Acute kidney injury (demeclocycline, mannitol, loop diuretics)
 - Chronic kidney disease (lithium)
 - Hypotension (mannitol, loop diuretics, vasopressin receptor antagonists)
 - Thirst (mannitol, loop diuretics, fluid restriction, vasopressin receptor antagonists)
 - Central nervous system symptoms (phenytoin)
 - Polyuria (mannitol, loop diuretics, vasopressin receptor antagonists)
 - Any other adverse event as reported by trialists
- Treatment discontinuation or switch

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register to 22 April 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

The Cochrane Renal Group's Specialised Register contains studies identified from the following sources:

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
- Weekly searches of MEDLINE OVID SP
- Handsearching of renal-related journals and the proceedings of major renal conferences
- Searching of the current year of EMBASE OVID SP
- Weekly current awareness alerts for selected renal journals
- Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTri-

als.gov.

Studies in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the specialised register section of information about the Cochrane Renal Group.

See **Appendix 1** for search terms used in strategies for this review.

Searching other resources

- Reference lists of clinical practice guidelines, review articles and relevant studies.
- Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
- Point-of-care sources such as Dynamed and UpToDate as well as US Food and Drug Administration (FDA) and European Medicines Agency (EMA) applications.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies possibly relevant to the review. The titles and abstracts were screened independently by two authors (EVN and MCH), who discarded studies that were not applicable; however studies and reviews that possibly included relevant data or information on studies of interest for our analysis were retained initially. Two authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions these data were used.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
 - Participants and personnel
 - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?

- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. death, number of patients with serum sodium concentration increase of ≥ 5 mmol/L, number of patients that develop hypernatraemia, number of patients with rapid increase in serum sodium concentration, number of patients that develop osmotic demyelination syndrome), individual study results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. length of hospital stay, serum sodium concentration at the end of the study or its change from beginning to the end of treatment), results were expressed as the mean difference (MD). For outcomes reported both as dichotomous and continuous data (thirst), we presented individual study results as odds ratios (OR), by converting standardized mean differences to the natural logarithm of the odds ratios as suggested by Chinn (Higgins 2011).

Unit of analysis issues

If studies had multiple treatment groups, we tried to collapse these into one where appropriate to enable single pair wise comparison (e.g. collapsing three groups of different doses of vasopressin receptor antagonists into one group and including them in single pair wise comparison versus placebo) (Higgins 2011).

Dealing with missing data

Any further information required from the original authors was requested by emailing the corresponding author. If no response or insufficient information was retrieved, we subsequently emailed the sponsor. Any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population was performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a χ^2 test on $N-1$ degrees of freedom, with an alpha of 0.05 used for statistical significance and with I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Funnel plots were used to assess for the potential existence of small study bias. If we suspected asymmetry on visual inspection and the analysis included >10 studies, we conducted formal hypothesis testing, using Egger's test for continuous outcomes and Peter's

regression test for dichotomous outcomes (Higgins 2011).

Data synthesis

Where feasible and appropriate, data were pooled using the random-effects model. Dichotomous outcome results were expressed as risk ratio (RR) and continuous outcome results were expressed as mean difference (MD), both with 95% confidence intervals. For outcomes reported both as dichotomous and continuous data (thirst), we converted standardized mean differences to log-transformed odds ratios, combined them using the generic inverse-variance method and expressed the overall effect estimate as an odds ratio with its 95% confidence interval (Higgins 2011). Although the underlying conditions causing hyponatraemia are very different, the mechanism by which hyponatraemia develops is similar in that vasopressin activity plays a role in most forms of the disorder. We believe it justified pooled analysis across subgroups of participants with different underlying conditions.

We summarised the quality of the evidence together with absolute treatment effects based on estimated baseline risks by using the Grading of Recommendations Assessment, Development, and Evaluation guidelines (Guyatt 2008). To estimate the absolute number of people with hyponatraemia who avoided death or incurred a rapid increase in serum sodium concentration with vasopressin receptor antagonists, the risk estimate and 95% CI were obtained from the control arm of the corresponding meta-analyses.

Subgroup analysis and investigation of heterogeneity

We analysed data for death, length of hospital stay, change from baseline and response in serum sodium concentration, cognitive function and outcomes related to overcorrection of serum sodium concentration within subgroups of participants dependent on the type of vasopressin receptor antagonist they were treated with. Additional prespecified subgroup analyses and univariate random effects meta-regression were conducted to explore potential sources of heterogeneity in effects of vasopressin receptor antagonists on death, change in serum sodium concentration and rapid increase in serum sodium concentration. The potential sources of heterogeneity included type of vasopressin receptor antagonist under evaluation, the underlying condition causing the hyponatraemia (with as non-prespecified categories studies only including participants with inappropriate antidiuresis; studies only including participants with heart failure or liver cirrhosis or studies including both), mean baseline serum sodium concentration, treatment duration and risk of selection bias. Meta-regression was undertaken on the log RR scale using Comprehensive Meta Analysis® software, each study weighting equal to the inverse of the variance of the estimate for that study, with between study variance estimated using the method of moments. Results were expressed as the ratio of the RR within each subgroup for categorical explanatory variables and per one unit increase for continuous variables.

Sensitivity analysis

In addition to estimating treatment effects using random effects models, we also estimated fixed effects models to ensure robustness of the model chosen and susceptibility to

outliers. Finally we also assessed whether including the number of deaths during follow-up (in contrast to only including those occurring during treatment) affected the estimate of the effect of treatment on all-cause mortality.

Results

Description of studies

Results of the search

We identified 1531 citations through electronic searches conducted in April 2015. We found 10 additional reports by screening the reference lists, contacting authors and con-

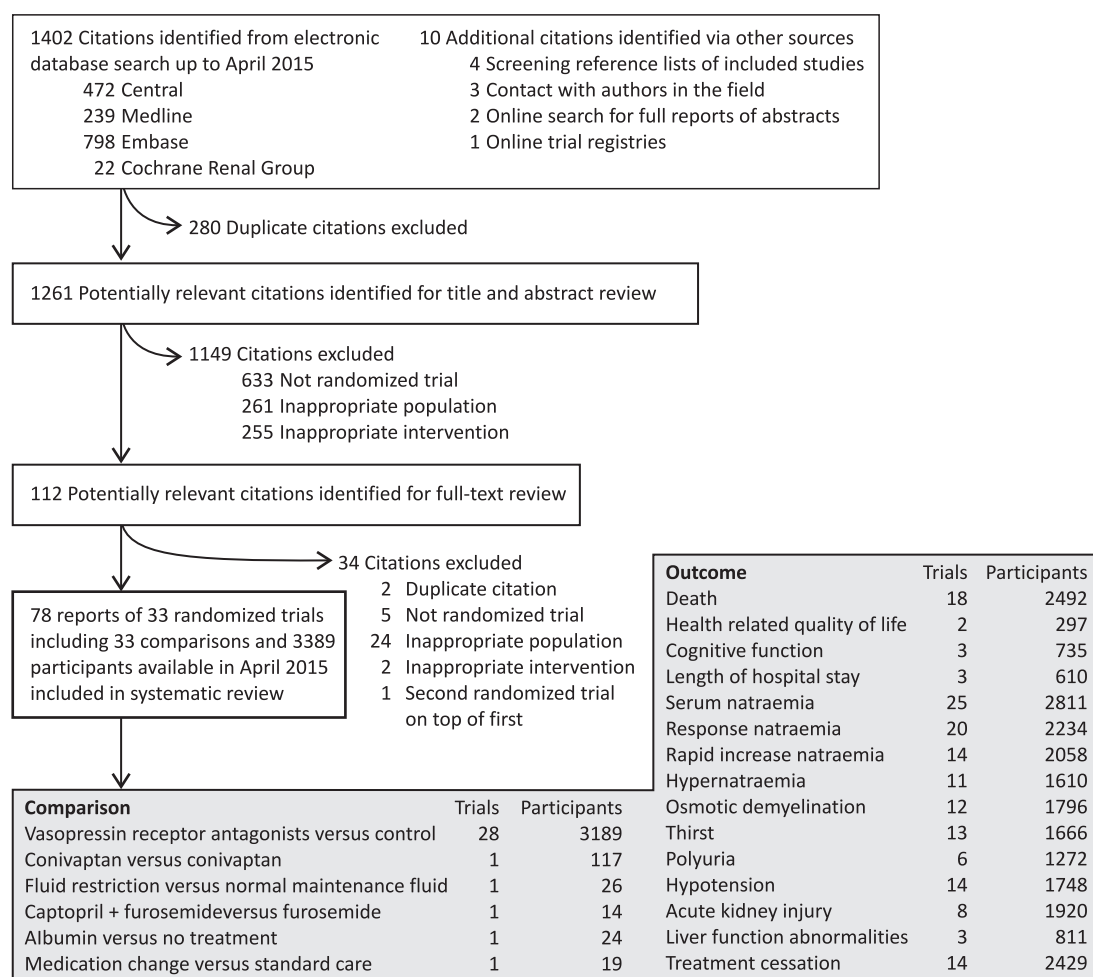


Figure 6.1. Study flow diagram.

ducting online searches for full reports of included abstracts. We reviewed in detail 112 reports, which led to the inclusion of 78 reports of 33 unique studies including 3389 participants (**Figure 6.1**).

Included studies

Twenty-eight studies (providing data for 3189 participants) compared a vasopressin receptor antagonist versus placebo, usual care or no treatment (ACTIV in CHF Study 2004; Annane 2009; BALANCE Study 2010; Decaux 2006; DILIPO Study 2011; EVEREST Study 2007; Ghali 2006; Gheorghiade 2003; Gines 2008; Gross 1999; HARMONY Study 2012; HYPOCAT Study 2008; INSIGHT Study 2007; Koren 2011; LIBRA Study 2012; Naidech 2010; Nevens 2009; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Salahudeen 2014; SALT-1 Study 2006; SALT-2 Study 2006; Soupart 2006; Wong 2003; Yang 2013; Zeltser 2007), or versus fluid restriction (Gheorghiade 2006). Studied vasopressin receptor antagonists included conivaptan (Annane 2009; Ghali 2006; Koren 2011; Naidech 2010; Zeltser 2007), lixivaptan (BALANCE Study 2010; Gross 1999; HARMONY Study 2012; LIBRA Study 2012; Wong 2003), satavaptan (Decaux 2006; DILIPO Study 2011; Gines 2008; HYPOCAT Study 2008; Soupart 2006), tolvaptan (ACTIV in CHF Study 2004; EVEREST Study 2007; Gheorghiade 2003; Gheorghiade 2006; INSIGHT Study 2007; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Salahudeen 2014; SALT-1 Study 2006; SALT-2 Study 2006; Yang 2013) and M0002 - also termed SPD556 or RWJ 351647 (Nevens 2009). One study assessed different doses of conivaptan (Kalra 2011).

One study (50 participants) compared fluid restriction with normal maintenance fluid in children with bacterial meningitis and reported data for the subgroup with hyponatraemia (26 participants) (Singhi 1995). One study (14 participants) compared captopril + furosemide versus furosemide alone (Dzau 1984) in adults with decompensated heart failure. One study (24 participants) compared infusion of human salt poor albumin in combination with fluid and sodium restriction versus fluid and sodium restriction alone in patients with liver cirrhosis and ascites (Jalan 2007). A final study (19 participants) compared a change in prescribed medications versus standard care in elderly patients admitted to the internal medicine ward or residents of the nursing home of the same institution (Peyro Saint Paul 2013).

Twenty-seven studies were conducted specifically in participants with hyponatraemia (LIBRA Study 2012; HARMONY Study 2012; Salahudeen 2014; Annane 2009; BALANCE Study 2010; Decaux 2006; Dzau 1984; Ghali 2006; Gheorghiade 2006; HYPOCAT Study 2008; Gines 2008; Gross 1999; INSIGHT Study 2007; Jalan 2007; Otsuka Study 2011c; Kalra 2011; Koren 2011; Otsuka Study 2011b; Naidech 2010; Nevens 2009; Peyro Saint Paul 2013; SALT-1 Study 2006; SALT-2 Study 2006; Soupart 2006; Wong 2003; Yang 2013; Zeltser 2007). For five studies, participants with hyponatraemia formed a subgroup of a larger study including both participants with and without hyponatraemia (DILIPO Study 2011; Gheorghiade 2003; ACTIV in CHF Study 2004; EVEREST Study 2007; Singhi 1995).

Studies included on average mostly older adults (median 65 years, interquartile range 5) with moderate hyponatraemia (median 129 mmol/L; range 124-133). Participants had

as primary cause of hyponatraemia a syndrome of inappropriate antidiuresis in nine studies (Decaux 2006; HARMONY Study 2012; LIBRA Study 2012; Naidech 2010; Otsuka Study 2011a; Peyro Saint Paul 2013; Salahudeen 2014; Singhi 1995; Soupart 2006), heart failure in seven studies (ACTIV in CHF Study 2004; BALANCE Study 2010; Dzau 1984; EVEREST Study 2007; Gheorghiade 2003; Otsuka Study 2011b; Yang 2013) and liver cirrhosis in five studies (Gines 2008; HYPOCAT Study 2008; Jalan 2007; Nevens 2009; Otsuka Study 2011c). The others included a mixed group of patients. Sample sizes varied and were generally small (median 69 participants; range 6 to 652). Treatment was mostly short-term (median 8 days; range 1 to 365). Data for at least one outcome of interest were available from 31 studies and 3365 participants, two studies reported no numeric data (Jalan 2007; Otsuka Study 2011c).

Excluded studies

We excluded 13 studies: three were not randomised trials but rather observational studies (Bichet 1999; Maji 2013; Zellweger 2001); eight did not include the appropriate population, with participants either not having hyponatraemia at randomisation (Albert 2013; De Vita 2012; Galton 2011; Mori 1999; Ramsay 1988; Zamboli 2011), or having hyponatraemia but caused by psychogenic polydipsia (Alexander 1991) or prolonged exercise (Rogers 2011); one randomised trial studied two different salt-restricted diets in combination with step-wise increase of diuretic treatment for reducing weight and ascites in patients with decompensated liver cirrhosis (Bernardi 1993); and finally one study (Gines 2007) would have led to double counting of participants as it represented a second randomised trial built on top of a first included study (HYPOCAT Study 2008) using the same study medication.

Risk of bias in included studies

The risk of bias is described in **Figure 6.2** and **Figure 6.3**.

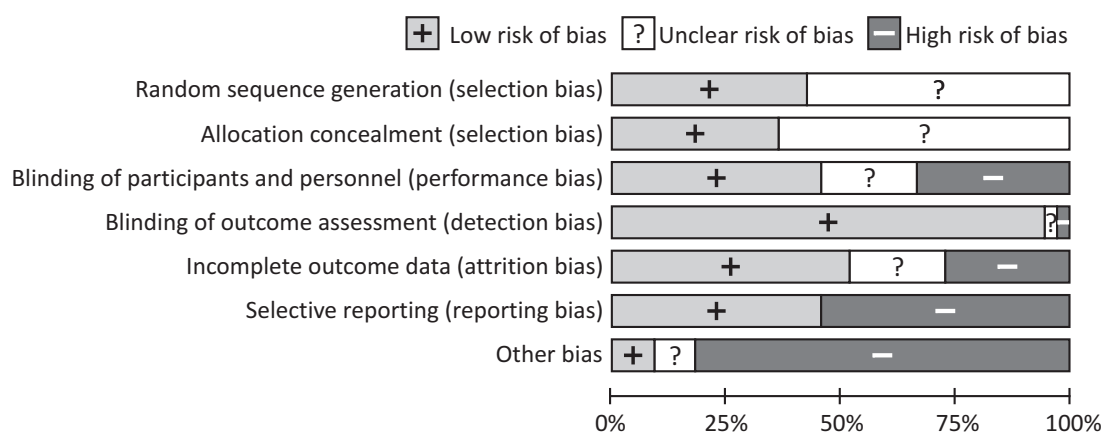


Figure 6.2. Risk of bias graph:

review authors' judgements about each risk of bias item presented as percentages across all included studies.

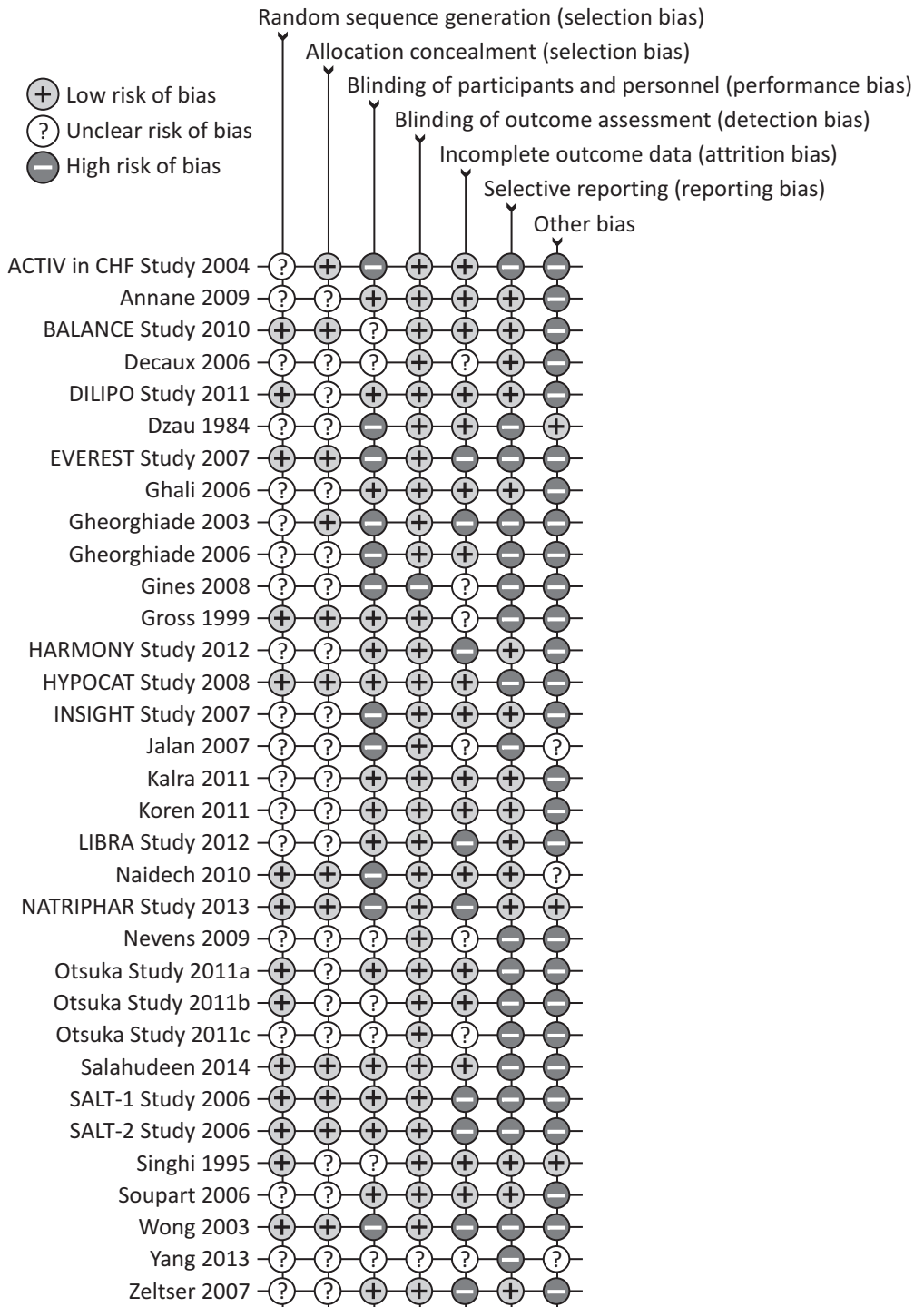


Figure 6.3. Risk of bias summary:

review authors' judgements about each risk of bias item for each included study.

Allocation (selection bias)

The allocation sequence was adequately generated in 14 studies (BALANCE Study 2010; DILIPO Study 2011; EVEREST Study 2007; Gross 1999; HYPOCAT Study 2008; Naidech 2010; Otsuka Study 2011a; Otsuka Study 2011b; Peyro Saint Paul 2013; Salahudeen 2014; SALT-1 Study 2006; SALT-2 Study 2006; Singhi 1995; Wong 2003), and adequately concealed in 12 studies (ACTIV in CHF Study 2004; BALANCE Study 2010; EVEREST Study 2007; Gheorghiade 2003; Gross 1999; HYPOCAT Study 2008; Naidech 2010; Peyro Saint Paul 2013; Salahudeen 2014; SALT-1 Study 2006; SALT-2 Study 2006; Wong 2003). For the remaining studies the authors provided insufficient information about the procedures to permit a judgement of the risk of bias.

Blinding (performance bias and detection bias)

In 26 studies, all assessing a vasopressin receptor antagonist, the investigators attempted to blind participants and personnel by providing a matching placebo (ACTIV in CHF Study 2004; Annane 2009; BALANCE Study 2010; Decaux 2006; DILIPO Study 2011; EVEREST Study 2007; Ghali 2006; Gheorghiade 2003; Gines 2008; Gross 1999; HARMONY Study 2012; HYPOCAT Study 2008; INSIGHT Study 2007; Kalra 2011; Koren 2011; LIBRA Study 2012; Nevens 2009; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Salahudeen 2014; SALT-1 Study 2006; SALT-2 Study 2006; Soupart 2006; Wong 2003; Zeltser 2007). Although it was probably unlikely for participants and personnel to be fully blinded due to important increases in urine output when treated with a vasopressin receptor antagonist, co-interventions of fluid restriction or salt-intake were reported and similar in 12 studies (Annane 2009; DILIPO Study 2011; Ghali 2006; Gross 1999; HARMONY Study 2012; HYPOCAT Study 2008; Kalra 2011; Koren 2011; LIBRA Study 2012; Salahudeen 2014; Soupart 2006; Zeltser 2007). For two studies, fluid restriction could be adapted by both participant and treating physician - e.g. based on urine output. We judged this would not have introduced important risk of bias for death and objective outcomes related to serum sodium concentration, but may have biased health-related quality of life measures and resulted in biased estimates of risk of rapid increase in serum sodium concentration (SALT-1 Study 2006; SALT-2 Study 2006).

Three studies explicitly reported blinding of outcomes assessors (BALANCE Study 2010; SALT-1 Study 2006; SALT-2 Study 2006). In 28 others we judged blinding of outcome assessors would likely have occurred or measured outcomes were objective enough so that the risk of bias was probably low (ACTIV in CHF Study 2004; Annane 2009; Decaux 2006; DILIPO Study 2011; Dzau 1984; EVEREST Study 2007; Ghali 2006; Gheorghiade 2003; Gheorghiade 2006; Gross 1999; HARMONY Study 2012; HYPOCAT Study 2008; INSIGHT Study 2007; Jalan 2007; Kalra 2011; Koren 2011; LIBRA Study 2012; Naidech 2010; Nevens 2009; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Peyro Saint Paul 2013; Salahudeen 2014; Singhi 1995; Soupart 2006; Wong 2003; Zeltser 2007).

Incomplete outcome data (attrition bias)

In 17 studies, attrition stayed below 20% with either well documented reasons and/or limited opportunity for important bias (ACTIV in CHF Study 2004; Annane 2009; BALANCE Study 2010; DILIPO Study 2011; Dzau 1984; Ghali 2006; Gheorghiad 2006; HYPOCAT Study 2008; INSIGHT Study 2007; Kalra 2011; Koren 2011; Naidech 2010; Otsuka Study 2011a; Otsuka Study 2011b; Salahudeen 2014; Singhi 1995; Soupart 2006). Eight studies had attrition rates >25% and either did not attempt to reinstate participants in the analysis (EVEREST Study 2007; Gheorghiad 2003 Peyro Saint Paul 2013) or used imputation methods to deal with missing serum sodium concentration values that may have caused overestimation of the effect of the study medication - e.g. last observation carried forward, thus ignoring rebound hyponatraemia on cessation of treatment (HARMONY Study 2012; LIBRA Study 2012; SALT-1 Study 2006; SALT-2 Study 2006; Wong 2003; Zeltser 2007). The others provided insufficient information to allow judgement of high or low risk of bias (Decaux 2006; Gheorghiad 2003; Gines 2008; Gross 1999; Jalan 2007; Nevens 2009; Otsuka Study 2011c; Yang 2013).

Selective reporting (reporting bias)

For 15 studies, we found a registered protocol in a trial registry (ACTIV in CHF Study 2004; BALANCE Study 2010; DILIPO Study 2011; EVEREST Study 2007; HARMONY Study 2012; HYPOCAT Study 2008; INSIGHT Study 2007; LIBRA Study 2012; Naidech 2010; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Peyro Saint Paul 2013; SALT-1 Study 2006; SALT-2 Study 2006). The Otsuka Study was registered as a single study but reported as three separate ones (Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c). Investigators fully reported all expected pre-registered outcomes at pre-registered time-points in two of those (INSIGHT Study 2007; Naidech 2010). Whether a protocol was provided or not, for 12 studies investigators reported all expected outcomes related to benefit and harms at reasonable time-points (Annane 2009; Decaux 2006; DILIPO Study 2011; Ghali 2006; HARMONY Study 2012; Kalra 2011; Koren 2011; LIBRA Study 2012; Peyro Saint Paul 2013; Singhi 1995; Soupart 2006; Zeltser 2007). In seven studies with treatment duration >1 week, authors did not report the primary outcomes all-cause mortality or health-related quality of life or any outcome related to rapid increases in serum sodium concentration (ACTIV in CHF Study 2004; Gheorghiad 2003; HYPOCAT Study 2008; Gines 2008; Nevens 2009; Salahudeen 2014; Yang 2013). In eight studies with treatment duration ≤1 week, authors did not report any secondary outcome related to serum sodium concentration or rapid increases thereof (Dzau 1984; Gheorghiad 2006; Gross 1999; Jalan 2007; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Wong 2003).

*Other potential sources of bias***Bias through possible financial conflict of interest of the authors and/or sponsorship bias**

Industry funded 27 studies (ACTIV in CHF Study 2004; Annane 2009; BALANCE Study

2010; Decaux 2006; DILIPO Study 2011; EVEREST Study 2007; Ghali 2006; Gheorghiade 2003; Gheorghiade 2006; Gross 1999; HARMONY Study 2012; HYPOCAT Study 2008; INSIGHT Study 2007; Kalra 2011; LIBRA Study 2012; Koren 2011; Naidech 2010; Nevens 2009; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Salahudeen 2014; Salahudeen 2014; SALT-1 Study 2006; SALT-2 Study 2006; Soupart 2006; Wong 2003; Zeltser 2007). The funding source was unclear for six studies (Dzau 1984; Gines 2008; Jalan 2007; Peyro Saint Paul 2013; Singhi 1995; Yang 2013). For 17 studies we retrieved a declaration of interest for the authors featuring on the reports (ACTIV in CHF Study 2004; Annane 2009; DILIPO Study 2011; EVEREST Study 2007; Ghali 2006; Gheorghiade 2003; Gines 2008; Gross 1999; HARMONY Study 2012; HYPOCAT Study 2008; Kalra 2011; Koren 2011; LIBRA Study 2012; Naidech 2010; SALT-1 Study 2006; SALT-2 Study 2006; Zeltser 2007). All save one (Naidech 2010) had author lists who featured people who had received money for presentations or consultancy, or were employed by the sponsor.

Effects of interventions

Vasopressin receptor antagonists versus placebo or no treatment

Primary outcomes

Vasopressin receptor antagonists had uncertain effects on mortality (Analysis 1.1, 15 studies, 2330 participants: RR 1.11, 95% CI 0.92 to 1.33; $I^2=0\%$). Vasopressin receptor antagonists slightly increased scores for the mental component summary of the Short Form Health Survey (SF-12) (Analysis 1.2, 2 studies, 297 participants: MD 4.76, 95% CI 0.11 to 9.41, $I^2=63\%$) and shortened hospital stay (Analysis 1.3, 3 studies, 610 participants: MD -1.63 days, 95% CI -2.96 to -0.30, $I^2=0\%$). Using GRADE criteria, we judged this evidence of low quality because study results possibly suffered from high risk of performance bias, attrition bias, selective outcome reporting bias, sponsorship bias or bias through possible financial conflict of interest of the authors.

Secondary outcomes

Vasopressin receptor antagonists caused a modest increase in serum sodium concentration. At the end of treatment, participants treated with placebo had an average increase in serum sodium concentration ranging from 0.5 to 4.7 mmol/L. In comparison, people treated with a vasopressin receptor antagonist had an average increase that was approximately 4 mmol/L higher (Analysis 1.4, 21 studies, 2641 participants: MD 4.15 mmol/L, 95% CI 3.13 to 5.17; $I^2=98\%$). These results were generally consistent for studies with shorter and longer follow-up. Although there was substantial heterogeneity among included studies as described by the I^2 , individual point estimates all favoured vasopressin receptor antagonists. Investigators often also analysed serum sodium concentration as a dichotomous outcome, defining response as an increase of 5 to 6 mmol/L or normalisation of the absolute value. Defined as such, the previous data translated into more than twice as many people having a response with vasopressin receptor antagonists compared with placebo (Analysis 1.5, 18 studies, 2104 participants: RR 2.58, 95% CI 2.00 to 3.33 $I^2=56\%$). On average 23% of partici-

pants treated with placebo had a response versus 60% treated with a vasopressin receptor antagonist. Overall, in absolute terms this implies treating 3 adults with hyponatraemia with a vasopressin receptor antagonist could result in one more individual attaining an increase in serum sodium concentration of 5 mmol/L. We judged the evidence to be of moderate quality due to risks of performance, attrition, selective reporting and sponsorship bias or bias through possible financial conflicts of interest of the study investigators.

Three studies evaluated cognitive function (BALANCE Study 2010; INSIGHT Study 2007; Salahudeen 2014). In a first study, using the trail making test part B, a neuropsychological test of visual attention and task switching, the investigators found lixivaptan did not shorten the time to complete the test (1 study, 652 participants: MD 13.60, 95% CI 12.82 to 14.38). A second study tested reaction time, psychomotor and processing speeds and found no difference in change between the groups (1 study, 56 participants, 0.20, 95% CI -0.10 to 0.50). The third study, assessing the change in mini mental state exam with tolvaptan, found no change from baseline (1 study, 30 participants, MD -0.70, 95% CI -2.23, 0.83).

Treatment with a vasopressin receptor antagonist raised the risk of rapid increases in serum sodium concentration by 67%, resulting in three additional people with a rapid increase per 100 treated with a vasopressin receptor antagonist versus placebo (Analysis 1.6, 14 studies, 2058 participants: RR 1.67, 95% CI 1.16 to 2.40; $I^2=0\%$). The analysis showed no significant heterogeneity. The effects for hypernatraemia were unclear (Analysis 1.7, 10 studies, 1595 participants: RR 1.37, 95% CI 0.63 to 3.01; $I^2=1\%$). None of the included studies reported participants developing osmotic demyelination syndrome.

Overall, treatment with vasopressin receptor antagonists increased the odds for thirst nearly three times compared versus treatment with placebo (Analysis 1.8, 13 studies, 1666 participants: OR 2.77, 95% CI 1.80 to 4.27; $I^2=66\%$). Other side-effects were generally less extensively reported. Nevertheless there was some evidence vasopressin receptor antagonists substantially increased the risk of polyuria (Analysis 1.9.1, 6 studies, 1272 participants: RR 4.69, 95% CI 1.59 to 13.85, $I^2=0\%$). The risks remained uncertain for hypotension (Analysis 1.9.2, 14 studies, 1748 participants: RR 1.11, 95% CI 0.75 to 1.63; $I^2=0\%$), acute kidney injury (Analysis 1.9.3, 8 studies, 1920 participants: RR 0.89, 95% CI 0.67 to 1.18; $I^2=0\%$) and liver function abnormalities (Analysis 1.9.4, 3 studies, 811 participants: RR 2.43, 95% CI 0.88 to 6.70). Half of the studies in which the vasopressin receptor antagonist was administered intravenously evaluated important adverse events related to the infusion itself. Overall there were almost three times as many patients developing infusion-site phlebitis (Analysis 1.10, 3 studies, 250 participants: RR 2.72, 95% CI 1.17 to 6.31; $I^2=0\%$); the effects for infusion-site thrombosis were less clear (Analysis 1.10, 3 studies, 250 participants: RR 1.45, 95% CI 0.25 to 8.55; $I^2=0\%$). There were slightly fewer people who discontinued treatment when given placebo than when given a vasopressin receptor antagonist (Analysis 1.11, 14 studies, 2429 participants: RR 0.93, 95% CI 0.85 to 1.00; $I^2=0\%$).

Analysis of heterogeneity

Using univariate metaregression and subgroup analyses, we explored possible sources of heterogeneity in the effect of vasopressin receptor antagonists on the change in serum sodium concentration. Our prespecified potential sources were: the specific vasopressin receptor antagonist compound, the underlying condition causing the hyponatraemia (with as non-prespecified categories studies only including participants with inappropriate antidiuresis; studies only including participants with heart failure or liver cirrhosis or studies including both), mean baseline serum sodium concentration, treatment duration and risk of selection bias as sources of heterogeneity. A higher serum sodium concentration at baseline resulted in smaller increases in serum sodium with treatment (**Figure 6.4**). Per 1 mmol/L increase in baseline serum sodium concentration between 124 and 133 mmol/L, the mean difference on average decreased from 5.7 by 0.33 mmol/L (95% CI -0.89 to -0.60) to 2.7 mmol/L. There was no evidence that the compound, the cause of hyponatraemia, the treatment duration or risk of selection bias modified the effect of vasopressin receptor antagonists on change from baseline in serum sodium concentration (**Table 6.1**).

We observed asymmetry in the funnel plot for the outcomes of response (Peters' regression test, $p=0.002$), suggesting the presence of small-study effects or publication bias, such

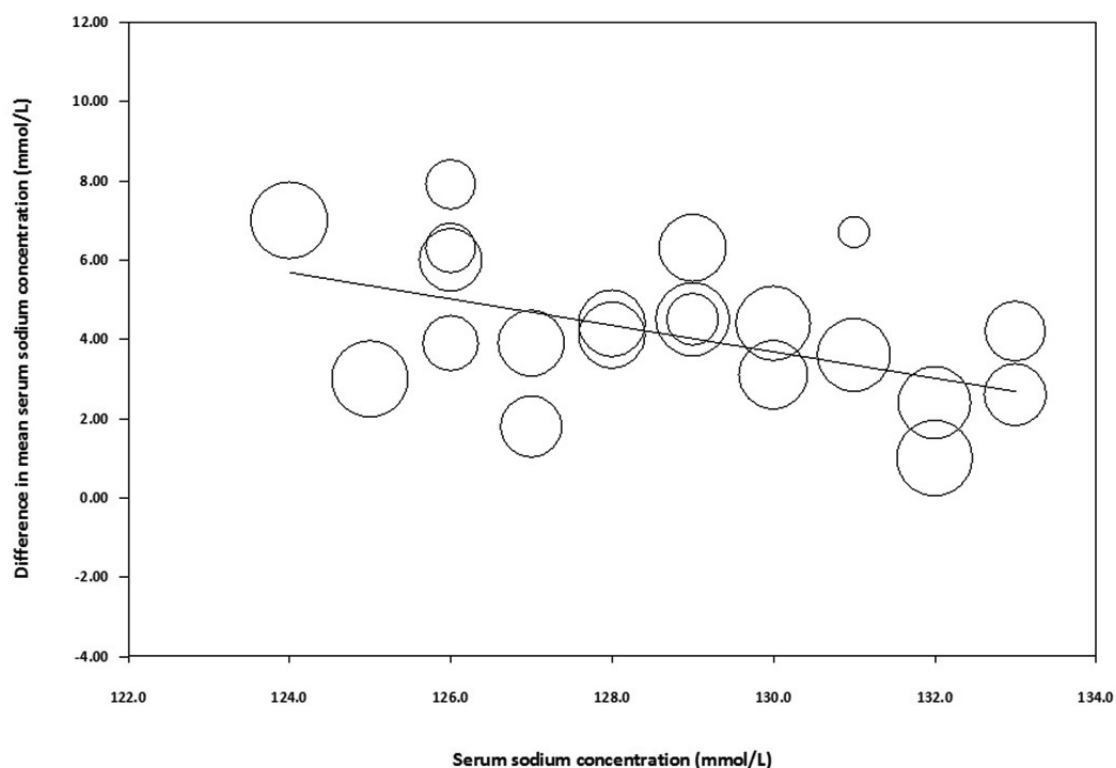


Figure 6.4. Effect of baseline serum sodium concentration on change in natraemia: metaregression.

Table 6.1. Metaregression.

Covariate	N	Scale	Proportional change in risk ratio or absolute change in mean difference	P value
Baseline serum sodium concentration	21	Per 1 mmol/L increase	-0.33 (-0.65 to -0.02)	0.04
Compound	21	Relative to conivaptan		0.17
Conivaptan	5		-	
Lixivaptan	4		-2.79 (-5.47 to -0.10)	
Satavaptan	3		-0.23 (-3.34 to 2.87)	
Tolvaptan	9		-0.82 (-3.13 to 1.50)	
Cause of hyponatraemia	21	Relative to SIAD		0.18
SIAD	5		-	
Combined SIAD - heart failure, cirrhosis	10		0.67 (-1.77 to 3.13)	
Heart failure	6		-1.19 (-3.84 to 1.47)	
Treatment duration	21	Per day increase	-0.02 (-0.04 to 0.00)	0.10
Risk of selection bias	21	Relative to low risk		0.86
Low risk	8		-	
High risk	13		0.18 (-1.90 to 2.27)	

that studies with small or null effects are not in the public domain and were not uncovered by our sensitive searching. Sensitivity analysis for this outcome excluding four studies with the largest effect estimates and largest estimate of variance reduced the relative risk with 30% (RR 2.07, 95%CI 1.67 to 2.56). However, the funnel plots for other related outcomes were more symmetrical. No asymmetry was observed in funnel plots for change and rapid increase in serum sodium concentration, thirst, treatment discontinuation, and data for death, length of hospital stay, cognitive function, hypernatraemia or other adverse events were insufficient to allow for detection of small-study effects.

Sensitivity analysis

Including the number of deaths occurring during follow-up rather than during treatment had little effect on the estimate of the treatment effect (Analysis 1.12, 16 studies, 2404 participants: RR 1.11, 95% CI 0.87 to 1.41).

For the serum sodium concentration analysis, when we excluded seven studies judged at high or unclear risk of performance bias, the summary treatment estimate remained unchanged (14 studies, 1458 participants: MD 4.89 mmol/L, 95% CI 4.02 to 5.76). When we excluded eight studies judged at high or unclear risk of attrition bias, we found similar treatment effect estimates (13 studies, 1342 participants: MD 4.71 mmol/L, 95% CI 3.34 to 6.08).

Conivaptan versus conivaptan

Kalra 2011 (117 participants) compared four regimens with or without a loading dose with one another and found no significant difference in any of the measured outcomes (death, change from baseline serum sodium concentration, response in serum sodium concentration, thirst, injection-site phlebitis, injection-site thrombosis, treatment discontinuation (data not shown).

Fluid restriction versus normal maintenance fluid treatment

Singhi 1995 (26 participants) compared fluid restriction (calculated as 65% of normal) versus normal maintenance intravenous fluid administration in children with bacterial meningitis. At two days, administration of restricted volumes significantly increased the serum sodium concentration (**Table 6.2**, 1 study, 26 participants: MD 4.40 mmol/L, 95% CI 1.79 to 7.01), but had uncertain effects on the risk of death (Table 6.1, 1 study, 26 participants: RR 7.80, 95% CI 0.46 to 131.62).

Captopril and furosemide versus captopril

Dzau 1984 (14 participants) found after five days of treatment, the combination of captopril and furosemide resulted in a 10 mmol/L higher serum sodium concentration compared with captopril alone (Table 6.2, 1 study, 14 participants, MD 10.00 mmol/L, 95% CI 8.60 to 11.40). The report did not include outcomes related to death, quality of life or adverse events due to rapid increases in serum sodium concentration caused by treatment.

Albumin versus no treatment

Jalan 2007 (24 participants) compared infusion of human salt poor albumin in combination with fluid and sodium restriction versus fluid and sodium restriction alone in patients with refractory ascites caused by liver cirrhosis. We only identified an abstract and it did not include comparative data.

Medication change versus standard care

Peyro Saint Paul 2013 (19 participants) compared a change in medication regimen to standard care in older adults suspected of having drug-induced hyponatraemia. Compared

Table 6.2. Single study results.

Comparison Outcome	Studies	Participants	Effect size, 95% CI
<i>Fluid restriction versus normal maintenance fluid treatment</i>			
Death	1	26	RR 7.80, 95% CI 0.46 to 131.62
Change from baseline serum sodium concentration	1	26	MD 4.40, 95% CI 1.79 to 7.01 mmol/L
<i>Captopril + furosemide versus furosemide</i>			
Serum sodium concentration	1	14	MD 10.00, 95% CI 8.60 to 11.40
<i>Medication change versus standard care</i>			
Death at 1 month	1	19	RR 0.37, 95% CI 0.02 to 8.01
Death at 3 months	1	14	RR 0.75, 95% CI 0.06 to 9.72
Change from baseline serum sodium concentration at 1 month	1	14	MD 1.70, 95% CI -1.39 to 4.79 mmol/L
Response in serum sodium concentration at 1 month	1	14	RR 10.11, 95% CI 0.68 to 150.68
Hyponatraemia at 1 month	1	14	Not estimable
Osmotic demyelinating syndrome	1	14	Not estimable

with standard care, changing the medication regimen had uncertain effects on risk of death (Analysis 5.1; 1 study, 19 participants: RR 0.37, 95% CI 0.02 to 8.01), response in serum sodium concentration (Analysis 5.3; 1 study 14 participants: RR 10.11, 95% CI 0.68 to 150.68) and change from baseline in serum sodium concentration at one month (Analysis 5.4, 1 study, 14 participants: MD 1.70, 95% CI -1.39 to 4.79). No participant in either group developed hyponatraemia or osmotic demyelination syndrome.

No studies evaluated the effects of urea, mannitol, corticosteroids, demeclocycline, lithium or phenytoin with regard to correction of hyponatraemia.

Discussion







Summary of main results (Table 6.3)

In low quality evidence from 21 randomised controlled trials involving 2641 participants, treatment of hyponatraemia with a vasopressin receptor antagonist modestly increased the serum sodium concentration (4 mmol/L) and slightly reduced hospital stay (-1.6 days), but had unclear effects on all-cause mortality, was associated with an increased risk of rapid serum sodium correction and commonly caused adverse effects such as thirst and polyuria. On average, treating 1,000 people would cause 290 additional people to have an increase in serum sodium concentration of at least 5 mmol/L, but it would come at a cost of an additional 29 people having an increase exceeding 10-12 mmol/L/day, generally considered as the threshold from which on there is an increased risk for osmotic demyelination. Effects were generally consistent across the different drugs in this class. The evidence on patient-important outcomes such as quality of life, cognitive and general functional status were limited and generally showed no important beneficial treatment effects. Despite the large patient population included, no cases of osmotic demyelination syndrome were reported. Randomized trial data for other interventions such as fluid restriction, urea, mannitol, loop diuretics, corticosteroids, demeclocycline, lithium and phenytoin were largely absent. As such, it remains unclear whether interventions aiming to raise serum sodium result in important health outcomes.

Overall completeness and applicability of evidence

Although the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved certain vasopressin receptor antagonists for treating people with hyponatraemia, regulatory approval was largely based on surrogate outcomes in short-term studies. To date, clinically important outcomes (e.g. reduction in all-cause mortality or improvement in quality of life, cognitive and general functional status) remain insufficiently investigated. The limited data we did have, suggested vasopressin receptor antagonists have little or no benefit on these outcomes for people with hyponatraemia. In the context of intervention studies, a surrogate is a measurable outcome such as a laboratory test, which responds to an intervention (e.g. lowering of cholesterol with statins) and is

Table 6.3. Summary of findings. Vasopressin receptor antagonists compared to placebo or no treatment for chronic non-hypovolaemic hypotonic hyponatraemia.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (Studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with Vasopressin receptor antagonists				
Death (Death) follow up: range 2 to 180 days	Study population		RR 1.11 (0.92 to 1.33)	2330 (15 RCTs)	 LOW ¹²	
	143 per 1000	159 per 1000 (132 to 190)				
Health-related quality of life (HRDOL) assessed with: Mental component score SF12 follow up: mean 30 days	The mean health-related quality of life in the control group was 0	The mean health-related quality of life in the intervention group was 4.76 higher (0.11 higher to 9.41 higher)	-	297 (2 RCTs)	 LOW ³	Scale 0 to 100 (worst to best)
Length of hospital stay (Hospital stay) follow up: range 1 to 2 years	The mean length of hospital stay in the control group was 6 to 11 days	The mean length of hospital stay in the intervention group was 1.58 lower (2.92 lower to 0.24 lower)	-	580 (2 RCTs)	 LOW ³	
Serum sodium concentration - continuous (Sodium - continuous) follow up: range 1 to 180 days	The mean serum sodium concentration - continuous in the control group was 0.3 to 4.8 mmol/L	The mean serum sodium concentration - continuous in the intervention group was 4.17 higher (3.18 higher to 5.16 higher)	-	2641 (21 RCTs)	 MODERATE ⁴	
Serum sodium concentration - dichotomous follow up: range 4 to 180 days	Study population		RR 2.25 (1.96 to 2.58)	2104 (18 RCTs)	 MODERATE ⁴	
	231 per 1000	521 per 1000 (454 to 597)				
Rapid sodium increase (Rapid sodium increase) follow up: range 1 to 5 days	Study population		RR 1.67 (1.16 to 2.40)	2058 (14 RCTs)	 MODERATE ¹	
	44 per 1000	73 per 1000 (51 to 105)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence;

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect;

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

causally associated a clinically important outcome (e.g. reduction in mortality with statins) (Ballinger 2014). Investigators often use surrogates instead of important health outcomes because surrogates can substantially reduce the cost, sample size and duration of a randomised trial. However, not all are valid proxies of clinically important outcomes. It is true that in acute and profound hyponatraemia, the evidence from observational studies is so overwhelming that we readily accept that increasing the serum sodium concentration is life-saving. It is also true that a chronically low serum sodium concentration is strongly and consistently associated with increased mortality and risk of bone fractures (Wald 2010). However, there is currently insufficient evidence that aside from affecting the surrogate (e.g. increase in serum sodium concentration with a vasopressin receptor antagonist) treatment in case of chronic hyponatraemia also changes the patient-centred outcomes downstream of the surrogate in the same causal pathway (e.g. reduction in mortality as a consequence of raising serum sodium concentration with a vasopressin receptor antagonist).

Studies contributing to this review included mostly participants with mild to moderate hyponatraemia (mean serum sodium concentration at study level ≥ 123 mmol/L). Meta-regression revealed a modifying effect of the serum sodium concentration at baseline, with lower values associated with larger increases in natraemia. Extrapolation of meta-regression data would suggest higher increases, but possibly higher risks of rapid correction as the baseline serum sodium decreases. Although no study reported osmotic demyelination, it is unclear what would happen if vasopressin receptor antagonists were used on a larger scale and in people with sodium concentrations below those included in the RCTs that contributed to this review.

Finally, studies evaluating the effectiveness of alternative interventions for increasing serum sodium concentration in people with chronic, non-hypovolaemic hyponatraemia are largely absent.

Quality of the evidence

Overall, according to GRADE criteria, data evaluating the effects of vasopressin receptor antagonists for people with chronic, non-hypovolaemic, hypotonic hyponatraemia on mortality, change and rapid increase in serum sodium concentration were of low quality. Low quality evidence suggests that additional studies are likely to change our confidence in the effects (Guyatt 2008). Although results were consistent among studies and we believed them to be generalizable to patients with hyponatraemia outside the RCT context, they were based on indirect and sometimes imprecise information obtained from surrogate outcomes. In addition, the estimates of treatment effect were derived from studies at generally high risk of bias. The quality of conduct and reporting of studies included in this review indeed was variable, with many studies omitting crucial methodological information used to assess the risk of bias. Importantly, all studies assessing benefits and harms of vasopressin receptor antagonists were likely instigated and sponsored by the pharmaceutical company

developing or seeking to commercialise the compound. For the studies that provided a declaration of interest for the authors of study reports, all save one had author lists who featured people who had received money for presentations or consultancy, or were employed by the sponsor. Empiric evidence shows that pharmaceutical industry-sponsored studies are more likely to have favourable efficacy results (risk ratio 1.32, 95% confidence interval 1.21 to 1.44) and harm results (risk ratio 1.87, 95% confidence interval 1.54 to 2.27) than studies not sponsored by industry (Lundh 2012). Data for other interventions such as fluid restriction, change in medical regimens, captopril or albumin were sparse and inconclusive.

Potential biases in the review process

Although this review was conducted by two or more independent authors, used a comprehensive search of the published and unpublished research designed by a specialist librarian, and examined all potentially relevant clinical outcomes, potential biases exist in the review process. The major weakness of this review is the paucity of data for treatments other than vasopressin receptor antagonists. First, summary of existing evidence therefore focusses the discourse on new, and expensive, treatments, rather than focusing on existing, and cheaper alternatives. Randomized trials are extraordinarily expensive and consequently often conducted by the pharmaceutical industry. This results in a catch-22 situation of evidence being mostly created, and thus only available, for newer interventions in general. Many other interventions are or have been used in clinical practice, but were driven to the background because randomised trial data were largely absent. Notably, also for fluid restriction, despite it being the currently accepted first-line treatment for both hypervolaemic and euvolaemic hyponatraemia, there are no randomised trial data available. Currently, there are limited opportunities for use of vasopressin receptor antagonists in practice. Only two vasopressin receptor antagonists have obtained large scale regulatory approval. Conivaptan is FDA approved for euvolaemic and hypervolaemic hyponatraemia in hospitalised patients. It is available only as an intravenous preparation and treatment duration is limited to a maximum duration of 4 days because of drug-interaction effects with other agents metabolized by the cytochrome P450 3A4 hepatic isoenzyme (FDA 2012). Tolvaptan, an oral agent, is also FDA approved for the treatment of euvolaemic and hypervolaemic hyponatraemia. In the European Union, tolvaptan is approved only for the treatment of euvolaemic hyponatraemia. Although theoretically available for long-term treatment, recent concerns around the potential for severe liver injury in patients with autosomal dominant polycystic kidney disease has caused the FDA to restrict the use of tolvaptan to 30 days and issue a contra-indication for patients with underlying liver disease (Samsca 2013).

Agreements and disagreements with other studies or reviews

This review largely agreed with the findings of two earlier systematic reviews. However, neither of these previous reviews sought to examine any other treatments beyond vasopressin receptor antagonists for treating chronic non-hypovolaemic hypotonic hyponatraemia.

mia. The first, including 15 RCTs and 1619 participants found vasopressin antagonists on average increased the serum sodium concentration by approximately 5 mmol/L at one week (13 studies, 1119 participants: MD 5.27 mmol/L, 95% CI 4.27 to 6.26), and approximately 3.5 mmol/L beyond the first week (8 studies, 793 participants: MD 3.49 mmol/L, 95% CI 2.56 to 4.41), but it came at a cost of increased risk of overly rapid correction of the serum sodium concentration (8 trials, 860 participants: RR, 2.52, 95% CI 1.26 to 5.08) (Rozen-Zvi 2010). The second review, including 11 RCTs and 1094 participants, found vasopressin antagonists on average increased the serum sodium concentration by approximately 5 mmol/L at day 4 (11 studies, 1094 participants: MD 4.90 mmol/L, 95% CI 4.10 to 5.80), but was associated with a 6% increased risk of overly rapid correction of the serum sodium concentration (9 studies, 995 participants: RD 0.06, 95% CI 0.03 to 0.10) (Jaber 2011).

We also largely agreed with the interpretation of these data by the respective study authors as presented in their discussion. However, we disagreed with the conclusion presented by Rozen-Zvi. We did not believe these data justified the conclusion that 'vasopressin receptor antagonists were effective for the treatment of hypervolaemic and euvolaemic hyponatraemia.' Although there is little doubt these agents increase the serum sodium concentration, this outcome needs to be weighed against the increased risk of an overly rapid correction and in itself is insufficient to conclude they will also improve the outcomes that matter to patients.

A recently published European guideline on the diagnosis and treatment of hyponatraemia stated in moderate or profound hyponatraemia, restricting fluid intake was first-line treatment (2D). In moderate or profound hyponatraemia, equal second-line treatments were: increasing solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral sodium chloride (2D). In moderate hyponatraemia, vasopressin receptor antagonists were not recommended (1C). In profound hyponatraemia, the guideline recommended against vasopressin receptor antagonists. In mild hyponatraemia the guideline suggested against treatment with the sole aim of increasing the serum sodium concentration (2C) (Spasovski 2014). In contrast to this, a largely American guideline published in 2013 projected vasopressin receptor antagonists were likely to become a mainstay of treatment for euvolaemic hyponatraemia and probably represented the best approach to treating hyponatraemia in most oedema-forming states (Verbalis 2013).

Authors' conclusions

Implications for practice

In people with chronic hyponatraemia, vasopressin receptor antagonists modestly raise serum sodium concentration at the cost of a 10% increased risk the increase being too rapid, and a subsequent small but unknown increased risk of osmotic demyelination syndrome. To date there is little evidence from RCTs for a beneficial effect on mortality, quality of life or any other truly important health outcome of these agents or in fact any other treatment for chronic hyponatraemia. It makes any recommendation problematic.

Implications for research

Further studies assessing commonly used treatments such as fluid restriction would inform practice and are warranted given limited evidence that in chronic hyponatraemia aside from affecting the surrogate (e.g. increase in serum sodium concentration) any treatment results in improved patient-centred outcomes and do not merely result in patients constantly feeling thirsty, thereby impairing their quality of life.

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Declarations of interest

Evi V Nagler, Maria C Haller, Wim Van Biesen and Raymond Vanholder are members of European Renal Best Practice (ERBP), the guidance producing body of the European Renal Association/ European Dialysis and Transplant Association (ERA-EDTA). ERBP has recently developed a clinical practice guideline on diagnosis and treatment of hyponatraemia in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine. ERBP receives their annual budget from the ERA-EDTA. The ERA-EDTA council does not interfere with topic choice or any other part of the guideline development process of ERBP.

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Differences between protocol and review

Liver function abnormalities were not anticipated as an adverse effect attributable to vasopressin receptor antagonists. A communication issued by Otsuka, indicating concerns around possibility for liver failure - be it in patients with autosomal polycystic kidney disease and at doses higher than those given for hyponatraemia - highlighted the outcome for inclusion in our review.

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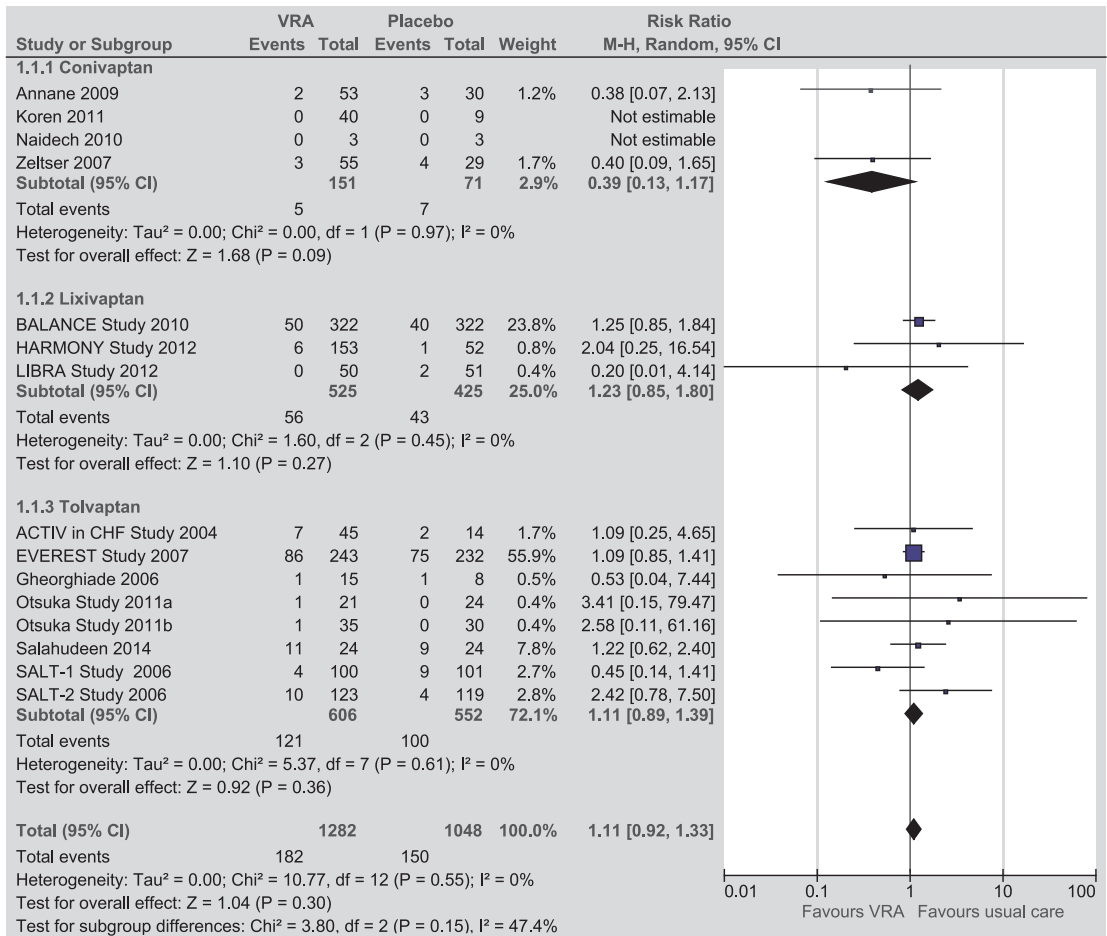
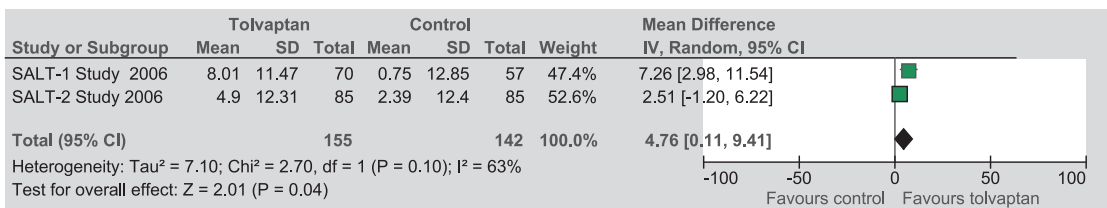
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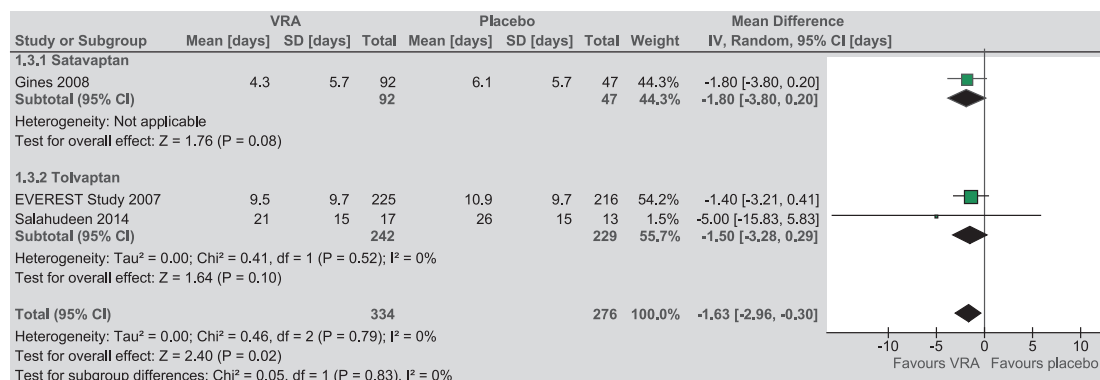
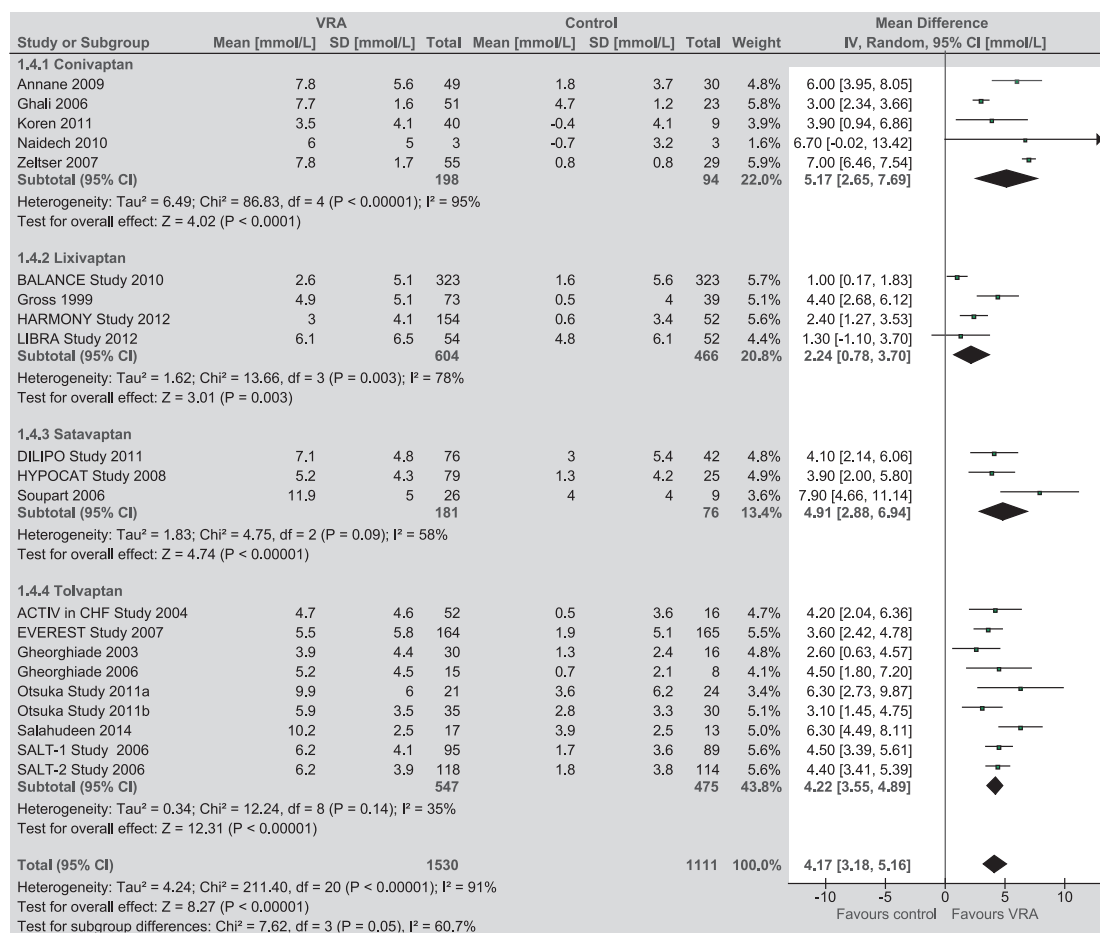
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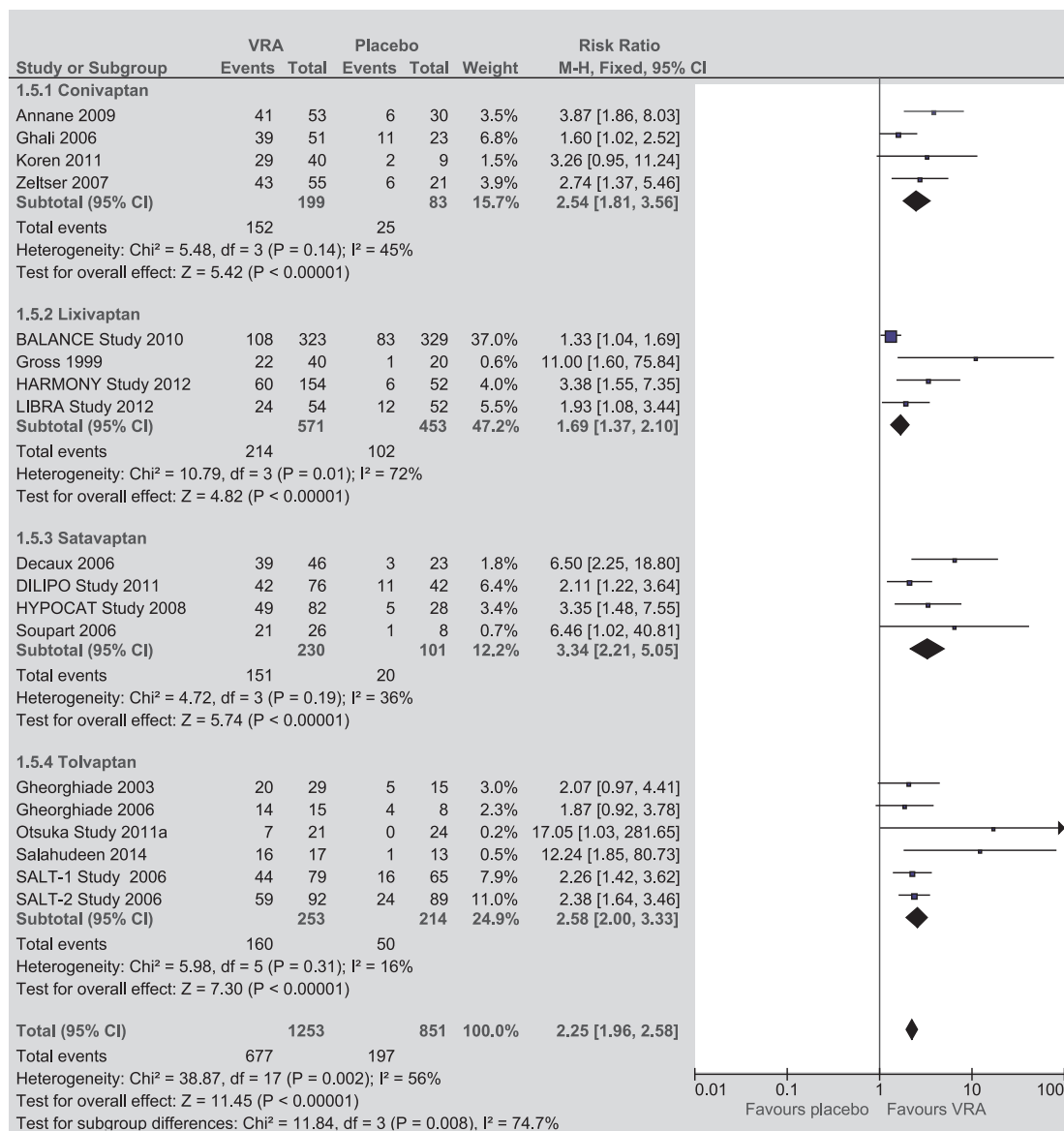
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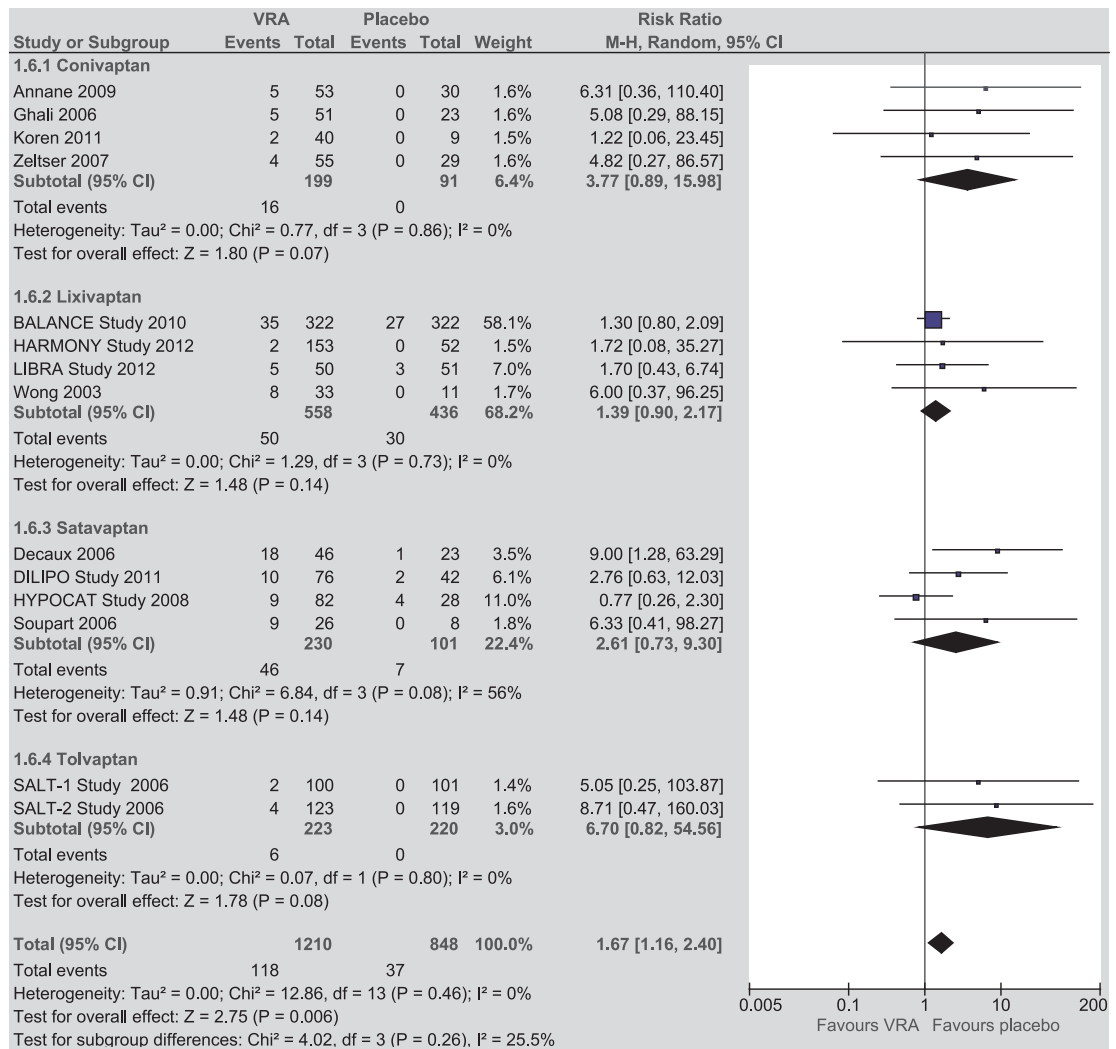
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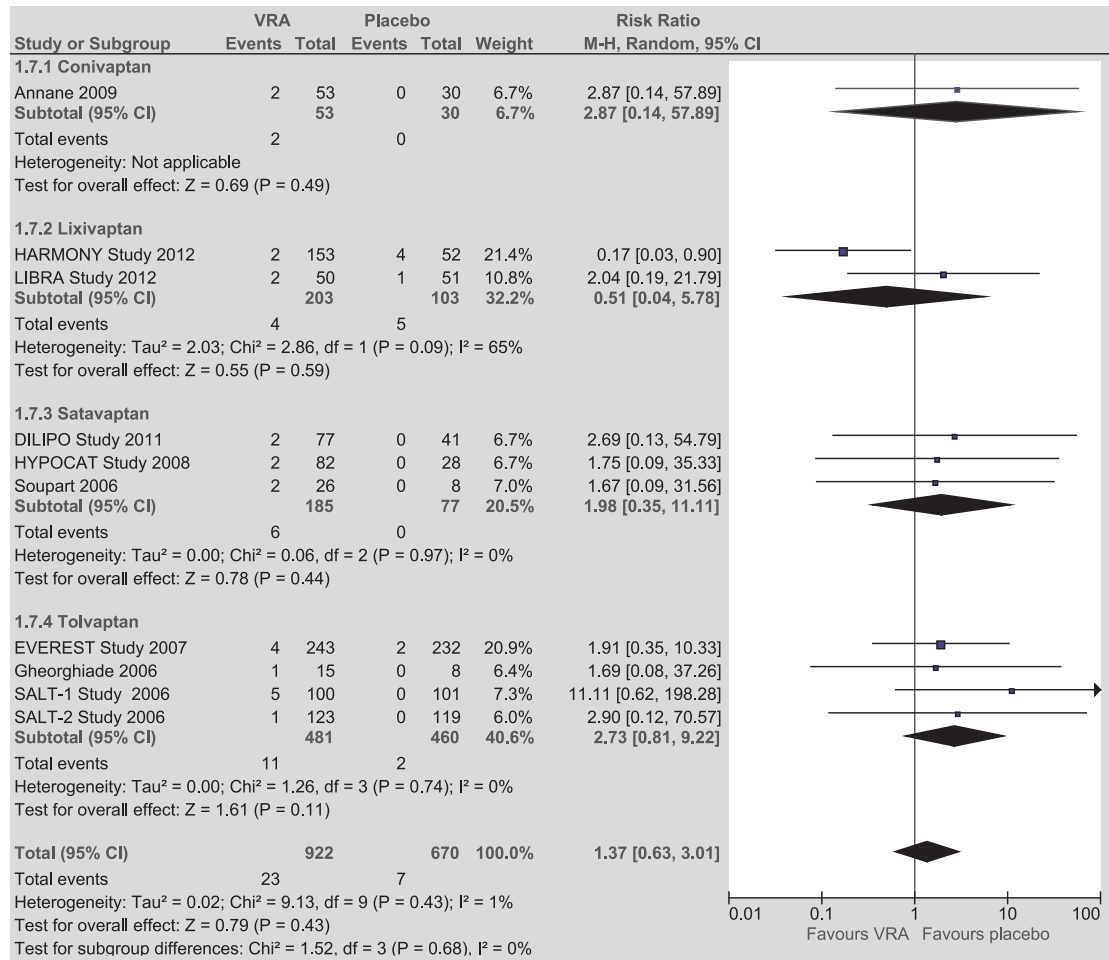
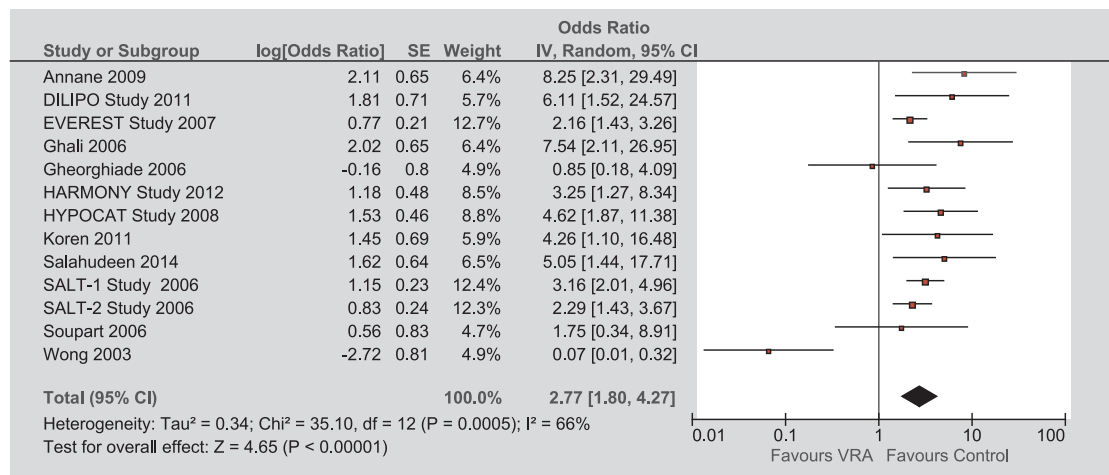
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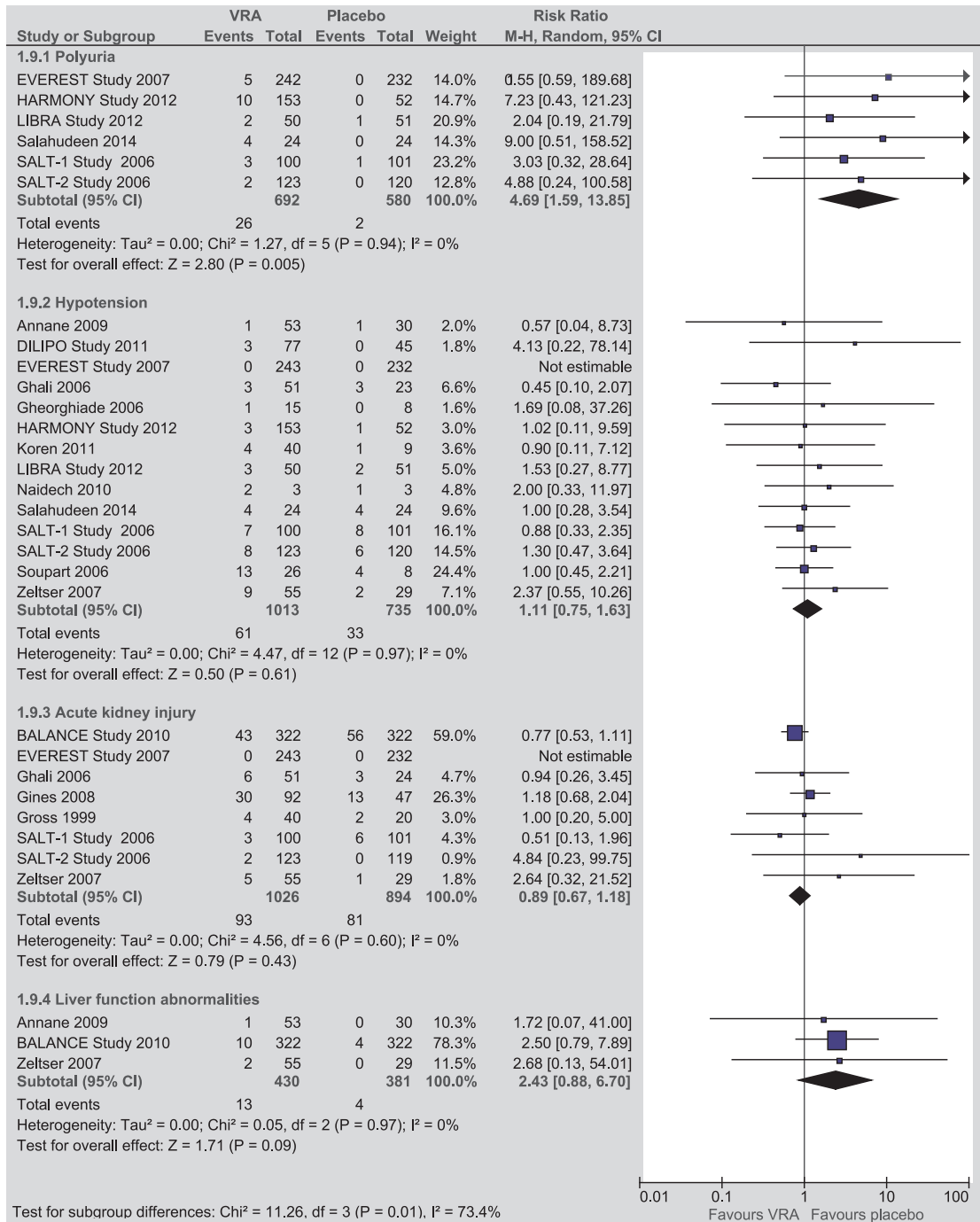
Data and analyses**Analysis 1.1. Death up to 6 months.****Analysis 1.2. Health-related quality of life**

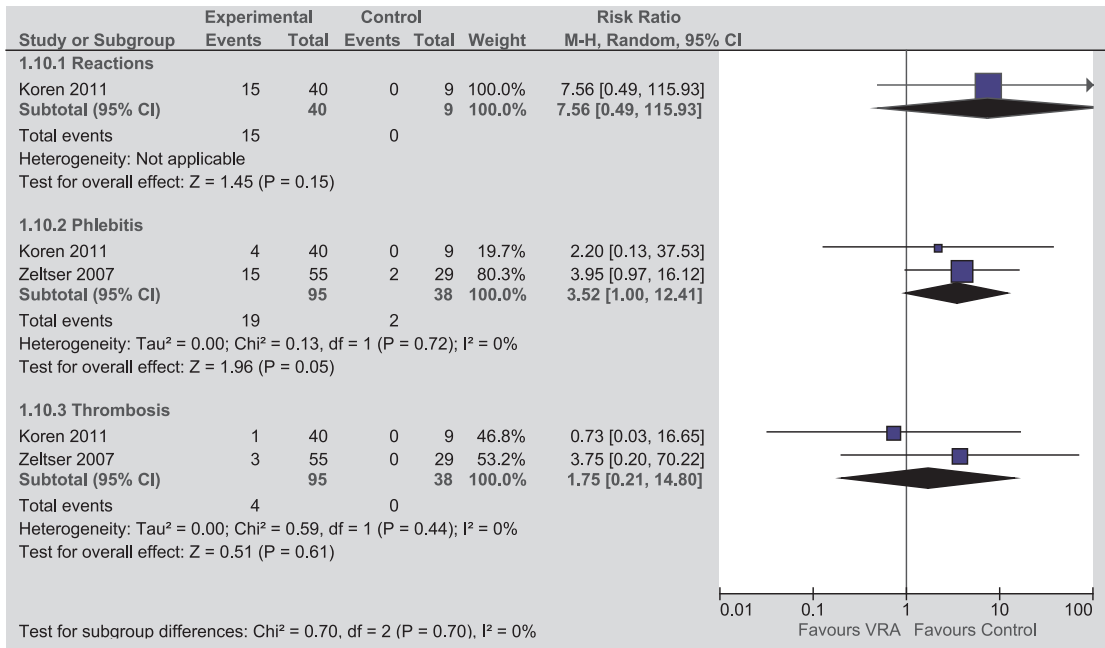
Analysis 1.3. Length of hospital stay.**Analysis 1.4. Change from baseline serum sodium concentration.**

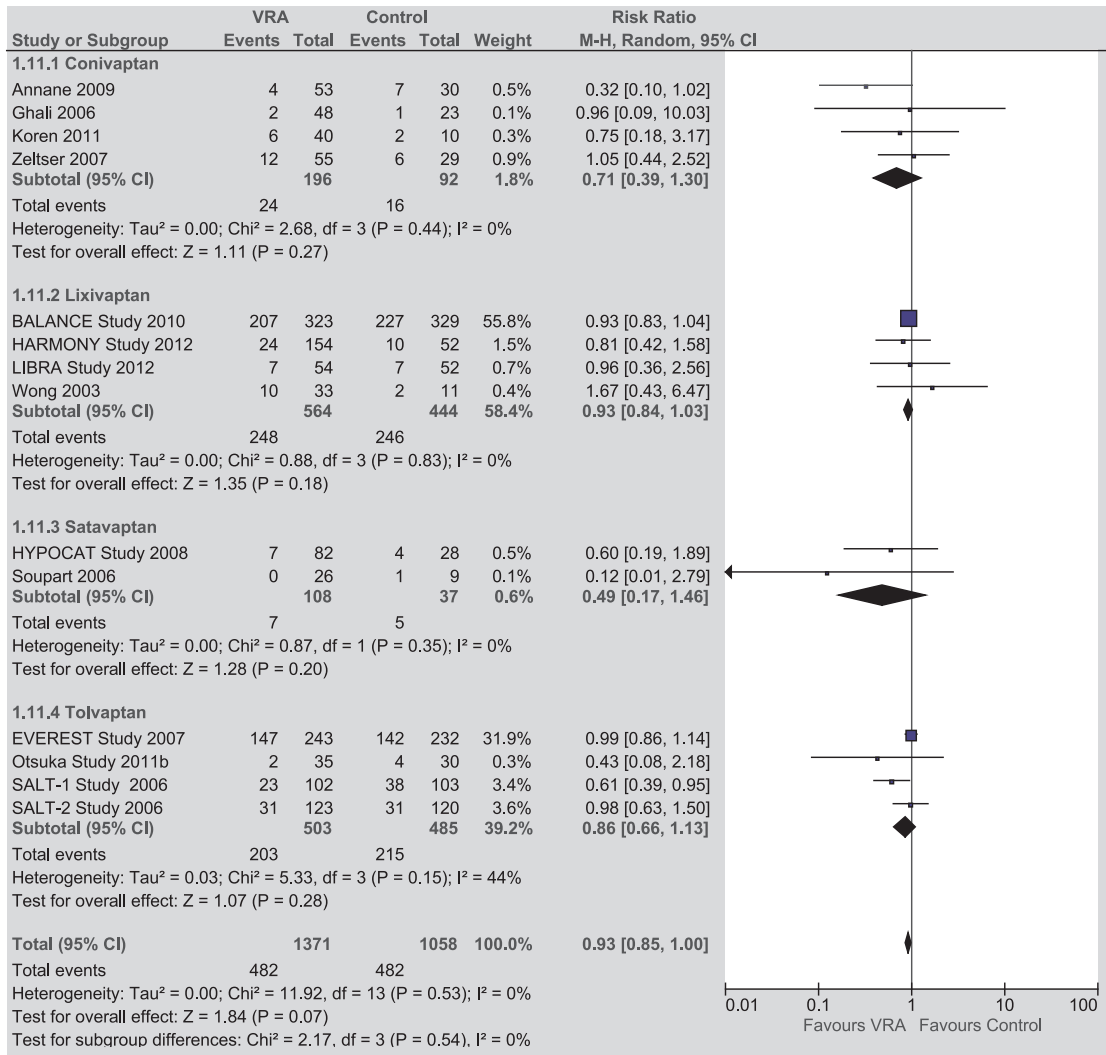
Analysis 1.5. Response in serum sodium concentration.

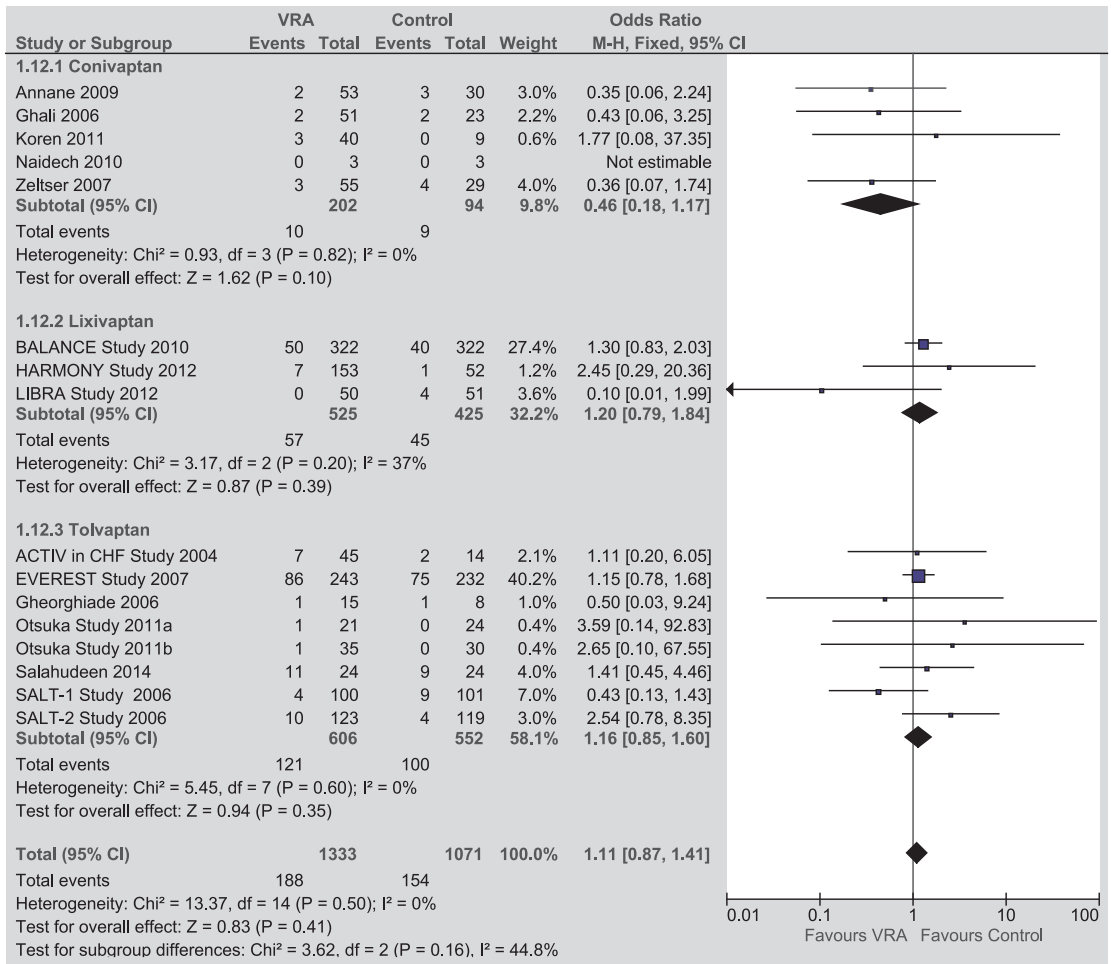
Analysis 1.6. Rapid increase in serum sodium concentration.

Analysis 1.7. Hypernatraemia during treatment.**Analysis 1.8. Thirst.**

Analysis 1.9. Other adverse events.

Analysis 1.10. Injection-site complications.

Analysis 1.11. Treatment discontinuation.

Analysis 1.12. Death during follow-up – sensitivity analysis.

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	hyponatr*emi*:ti,ab,kw "inappropriate ADH syndrome":ti,ab,kw "inappropriate vasopressin secretion":ti,ab,kw {or #1-#3}
MEDLINE	Hyponatremia/ Inappropriate ADH Syndrome/ hyponatr?emi*.tw. inappropriate ADH syndrome.tw. inappropriate vasopressin secretion.tw. or/1-5
EMBASE	hyponatremia/ inappropriate vasopressin secretion/ hyponatr?emi*.tw. inappropriate ADH syndrome.tw. inappropriate vasopressin secretion.tw. or/1-5

European clinical practice guideline on diagnosis and treatment of hyponatraemia

*In memory of Prof. dr. Bruno Allolio,
valued member of the guideline development group,
who shall be sorely missed*

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn E, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol Dial Transplant 2014, doi: 10.1093/ndt/gfu040

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Abstract

Hyponatraemia, defined as a serum sodium concentration <135 mmol/l, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening, and is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Despite this, the management of patients remains problematic. The prevalence of hyponatraemia in widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution- and speciality-based approaches to diagnosis and treatment. To obtain a common and holistic view, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP), have developed the Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia as a joint venture of three societies representing specialists with a natural interest in hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focused on patient-important outcomes and included utility for clinicians involved in everyday practice.

Foreword

Hyponatraemia is a clinical feature in 15–20% of emergency admissions to hospital. It is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Hyponatraemia is therefore both common and important.

Despite this, the management of patients remains problematic. The prevalence of hyponatraemia under widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds have fostered diverse institution- and speciality-based approaches to diagnosis and treatment. However, the paucity of well-designed, prospective studies in the field has limited the evidence-base to these approaches. Previous guidance has often been based on experience or practice, without a systematic approach to evaluation and lacking a clear, patient-centred focus. Clinicians using previous guidance may have noted a number of problems:

It has been difficult to follow the guidance in day-to-day clinical practice, especially by doctors in training who are managing patients in the 'front line'. Here, the requirement is for clear, concise and practical advice on what has to be done, including during the critical 'out-of-office hours' period. Complex diagnostic algorithms and time-consuming investigations are real barriers to implementation in this context.

The guidance has been over-simplistic and does not reflect the range of clinical problems encountered in day-to-day practice.

The guidance has been limited by a diagnosis-, mechanism- or duration-based approach to treatment, failing to recognise that establishing the diagnosis, mechanism or duration of hyponatraemia may be difficult. Previous guidance has mostly used duration of hyponatraemia as a key point on which to base management. Yet, duration can be hard to establish, especially in emergency settings. Decisions often have to be made on limited information.

The guidance has demonstrated an institutional or specialty-specific bias, limiting implementation across sites and clinical disciplines. This is best demonstrated in institution- or speciality-specific approaches to investigations.

The guidance has used a biochemical focus, failing to prioritise clinical status in decisions on treatment options. Clinicians know that the degree of biochemical hyponatraemia does not always match the clinical state of the patient. Guidance that bases management advice simply on the serum sodium concentration may be counter to clinical experience, risking credibility and engagement.

Together, these factors have limited the utility of previous advice. Two emerging themes require that we revisit the area:

- The clear recognition of the importance of evidence-based approaches to patient care to enhance quality, improve safety and establish a clear and transparent framework for service development and healthcare provision.
- The advent of new diagnostics and therapeutics, highlighting the need for a valid, reliable and transparent process of evaluation to support key decisions.

To obtain a common and holistic view, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP), have developed new guidance on the diagnostic approach and treatment of hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure that the document focused on patient-important outcomes and included utility for clinicians involved in everyday practice.

Composition of the guideline development group

A steering committee with representatives of all the three societies convened in October 2010 and decided on the composition of the Guideline Development Group, taking into account the clinical and research expertise of each proposed candidate.

Guideline development group co-chairs

- Goce Spasovski
Consultant Nephrologist, State University Hospital Skopje, Skopje, Macedonia.
- Raymond Vanholder
Consultant Nephrologist, Ghent University Hospital, Ghent, Belgium.

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Purpose and scope of this guideline

Why was this guideline produced?

The purpose of this Clinical Practice Guideline was to provide guidance on the diagnosis and treatment of adult individuals with hypotonic hyponatraemia. It was designed to provide information and assist in decision-making related to this topic. It was not intended to define a standard of care and should not be construed as one. It should not be interpreted as prescribing an exclusive course of management.

This guideline was developed as a joint venture of three societies representing specialists with a natural interest in hyponatraemia: the ESICM, the ESE and the ERA-EDTA, represented by ERBP.

All three societies agreed that there was a need for guidance on diagnostic assessment and therapeutic management of hyponatraemia. A recent systematic review, which included three clinical practice guidelines and five consensus statements, confirmed the lack of high-quality guidelines in this field [1]. The guidance documents scored low to moderate in the six domains of the AGREEII tool – scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence – and the management strategies proposed in the different guidance documents were sometimes contradictory [2].

Who is this guideline for?

This guideline was meant to support clinical decision-making for any healthcare profes-

sional dealing with hyponatraemia, i.e. general practitioners, internists, surgeons and other physicians dealing with hyponatraemia in both an outpatient and an in-hospital setting. The guideline was also developed for policymakers for informing standards of care and for supporting the decision-making process.

What is this guideline about?

This section defines what this guideline intended to cover and what the guideline developers considered. The scope was determined at a first meeting held in Barcelona in October 2010 with representatives of ESICM, ESE and ERBP present.

Population

The guideline covers hyponatraemia in adults through the biochemical analysis of a blood sample. It does not cover hyponatraemia detected in children because the guideline development group judged that hyponatraemia in children represented a specific area of expertise. The guideline also does not cover screening for hyponatraemia.

Conditions

The guideline specifically covers diagnosis and management of true hypotonic hyponatraemia. It covers the differentiation of hypotonic hyponatraemia from non-hypotonic hyponatraemia but does not deal with the specific diagnostic and therapeutic peculiarities in the setting of pseudo-hyponatraemia, isotonic or hypertonic hyponatraemia. These situations are not associated with the hypotonic state responsible for the majority of symptoms attributable to true hypotonic hyponatraemia. The guideline covers diagnosis and management of both acute and chronic hypotonic hyponatraemia in case of reduced, normal and increased extracellular fluid volume. It does not cover the diagnosis or treatment of the underlying conditions that can be associated with hypotonic hyponatraemia.

Healthcare setting

This guideline targets primary, secondary and tertiary settings dealing with diagnostic testing and the management of hyponatraemia in adults.

Clinical management

This guideline deals with diagnostic tools for improving accuracy of the differential diagnosis of hypotonic hyponatraemia, allowing more specific treatment strategies tailored to the underlying cause and/or pathophysiological mechanism.

This guideline covers the treatment for adults with acute or chronic, symptomatic or asymptomatic hypotonic hyponatraemia, regardless of the underlying condition.

Methods for guideline development

Establishment of the guideline development group

The councils of the three participating societies, ESICM, ESE and ERBP, selected the co-chairs of the guideline development group. The co-chairs then assembled the steering committee with representatives of the three societies involved in this joint venture. This steering committee convened in October 2010 and decided on the composition of the guideline development group, taking into account the clinical and research expertise of the proposed candidates. The guideline development group consisted of content experts, which included individuals with expertise in hyponatraemia, endocrinology, general internal medicine, intensive care medicine and clinical nephrology as well as an expert in systematic review methodology. The ERBP methods support team provided methodological input and practical assistance throughout the guideline development process.

Developing clinical questions

From the final scope of the guideline, specific research questions, for which a systematic review would be conducted, were identified.

Diagnosis and differential diagnosis of hypotonic hyponatraemia

- In patients with hypotonic hyponatraemia, how accurate are various 'diagnostic strategies' in comparison with a reference test of infusing 2 l 0.9% sodium chloride solution for differentiating hypovolaemic from euvolaemic hyponatraemia?
- In patients with hypotonic hyponatraemia, how accurate are various 'diagnostic strategies' in comparison with a reference test of expert panel diagnosis in differentiating hypovolaemic from euvolaemic hyponatraemia?

Acute and chronic treatment of hypotonic hyponatraemia

- In patients with hypotonic hyponatraemia, which treatments are effective in improving outcomes?
- In patients with hypotonic hyponatraemia, does the change in serum sodium concentration per unit time influence outcomes?

Development of review questions

The methods support team assisted in developing review questions, i.e. framing the clinical questions into a searchable format. This required careful specification of the patient group (P), the intervention (I), the comparator (C) and the outcomes (O) for intervention questions and the patient group, index tests, reference standard and target condition for questions of diagnostic test accuracy [3]. For each question, the guideline development group agreed on explicit review question criteria including study design features (See Ap-

pendices 1 and 2 for Detailed Review Questions and PICO tables. See section on Appendix given at the end of this article).

Assessment of the relative importance of the outcomes

For each intervention question, the guideline development group compiled a list of outcomes, reflecting both benefits and harms of alternative management strategies. The guideline development group ranked the outcomes as critically, highly or moderately important according to their relative importance in the decision-making process. As such, patient-important health outcomes related to hyponatraemia and the treatment for hyponatraemia were considered critical. Owing to its surrogate nature, the outcomes 'change in serum sodium concentration' and 'correction of serum sodium concentration' were considered less important than the critically and highly important clinical outcomes (**Table 7.1**).

Table 7.1. *Hierarchy of outcomes.*

Hierarchy	Outcomes
Critically important	Patient survival
	Coma
	Brain damage/brain oedema
	Epileptic seizures
	Osmotic demyelinating syndrome
	Respiratory arrest
	Quality of life
	Cognitive function
Highly important	Bone fractures
	Falls
	Length of hospital stay
Moderately important	Serum sodium concentration

Target population perspectives

An effort was taken to capture the target population's perspectives by adopting two strategies. First, ERBP has a permanent patient representative in its board. Although he was not included in the guideline development group or in the evidence review process, drafts of the guideline document were sent for his review and his comments were taken into account in revising and drafting the final document.

Secondly, the guideline underwent public review before publication. The guideline was sent to the council of two different societies for each specialty involved: for ESICM, the Australian and New Zealand Intensive Care Society (ANZICS) and American Society of Critical Care Medicine (SSCM); for ESE, the Endocrine Society of Australia (ESA) and the Endocrine Society (USA); and for ERBP, the Kidney Health Australia–Caring for Australasians with Renal Impairment (KHA–CARI) and the American Society of Nephrology (ASN). Each of these societies was specifically asked to indicate two to three reviewers. Reviewers could use free text to suggest amendments and/or fill in a matrix questionnaire in Microsoft Excel. All members

of the ERA–EDTA received an online questionnaire with a standardised answer form in Microsoft Excel. ERA–EDTA members were asked to express to what extent they judged the individual statements were clear and implementable and to what extent they agreed with the content. In addition, a free text field was provided to allow for additional comments.

Searching for evidence

Sources

The ERBP methods support team searched The Cochrane Database of Systematic Reviews (May 2011), DARE (May 2011), CENTRAL (May 2011) and MEDLINE (1946 to May, week 4, 2011) for questions on both diagnosis and treatment. To identify the limits for the increase in serum sodium concentration above which the risk of osmotic demyelination starts to rise, we searched MEDLINE database from 1997 onwards under the assumption that earlier reports would describe more dramatic increases and would not contribute to helping us set an upper limit. All searches were updated on 10th December 2012. The search strategies combined subject headings and text words for the patient population, index test and target condition for the diagnostic questions and subject headings and text words for the population and intervention for the intervention questions. The detailed search strategies are available in Appendix 3, see section titled Appendix given at the end of this article.

Reference lists from included publications were screened to identify additional papers. The methods support team also searched guideline databases and organisations including the National Guideline Clearinghouse, Guidelines International Network, Guidelines Finder, Centre for Reviews and Dissemination, National Institute for Clinical Excellence, and professional societies of Nephrology, Endocrinology and Intensive Care Medicine for guidelines to screen the reference lists.

Selection

For diagnostic questions, we included every study that compared any of the predefined clinical or biochemical tests with infusion of 2 l 0.9% saline as a reference test or with an expert panel for differentiating hypovolaemic from euvolaemic hyponatraemia. For questions on treatment strategies, we included every study in which one of the predefined medications was evaluated in humans. We excluded case series that reported on benefit if the number of participants was ≤ 5 but included even individual case reports if they reported an adverse event. No restriction was made based on language. For identifying the limits for the increase in serum sodium concentration above which the risk of osmotic demyelination starts to rise, we included all observational studies reporting cases of osmotic demyelinating syndrome and corresponding serum sodium concentration correction speeds.

A member of the ERBP methods support team screened all titles and abstracts to discard the clearly irrelevant ones. All members of the guideline development group completed a

second screening. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by group consensus.

The methods support team retrieved full texts of potentially relevant studies and two reviewers examined them for eligibility independently of each other. The reviewer duos always consisted of one content specialist and one methodologist from the ERBP methods support team. Any discrepancies were resolved by consensus. If no consensus could be reached, the disagreement was settled by group arbitration.

Data extraction and critical appraisal of individual studies

For each included study, we collected relevant information on design, conduct and relevant results through standardised data extraction forms in Microsoft Excel (2010). As part of an ongoing process of introducing software to facilitate the guideline development process, the ERBP methods support team used two formats for data extraction and collation. For detailed methods, see Appendices 4 and 5, see section titled Appendix given at the end of this article. Briefly, we used both a simple spreadsheet format and a more sophisticated version, which incorporated user forms programmed in Visual Basic. For each question, two reviewers extracted all data independently of each other. We produced tables displaying the data extraction of both reviewers. Both reviewers checked all data independently of each other. Any discrepancies were resolved by consensus and if no consensus could be reached, disagreements were resolved by an independent referee. From these tables, we produced merged consensus evidence tables for informing the recommendations. The evidence tables are available in Appendices 6 and 7, see section titled Appendix given at the end of this article.

Risk of bias of the included studies was evaluated using various validated checklists, as recommended by the Cochrane Collaboration. These were AMSTAR for Systematic Reviews [4], the Cochrane Risk of Bias tool for randomised controlled trials [5], the Newcastle Ottawa scale for cohort and case-control studies [6] and QUADAS for diagnostic test accuracy studies [7]. Data were compiled centrally by the ERBP methods support team.

Evidence profiles

The evidence for outcomes on therapeutic interventions from included systematic reviews and randomised controlled trials was presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (<http://www.gradeworkinggroup.org/>). The evidence profiles include details of the quality assessment as well as summary – pooled or un-pooled – outcome data, an absolute measure of intervention effect when appropriate and the summary of quality of evidence for each outcome. Evidence profiles were constructed by the methods support team and reviewed and confirmed with the rest of the guideline development group. Evidence profiles were constructed for research questions addressed by at least two randomised controlled trials. If the body of evidence for a particular comparison of interest consisted of only one randomised controlled trial or of solely observational data,

the summary tables provided the final level of synthesis.

Rating the quality of the evidence for each outcome across studies

In accordance with GRADE, the guideline development group initially categorised the quality of the evidence for each outcome as high if it originated predominantly from randomised controlled trials and low if it originated from observational data. We subsequently downgraded the quality of the evidence one or two levels if results from individual studies were at serious or very serious risk of bias, there were serious inconsistencies in the results across studies, the evidence was indirect, the data were sparse or imprecise or publication bias thought to be likely. If evidence arose from observational data, but effect sizes were large, there was evidence of a dose–response gradient or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect, we would upgrade the quality of the evidence (**Table 7.2**). Uncontrolled case series and case reports automatically received downgrading from low to very low level of evidence for risk of bias, so that no other reasons for downgrading were marked. By repeating this procedure, we would obtain an overall quality of the evidence for each outcome and each intervention. For list of definitions, see **Table 7.3**.

Table 7.2. Method of rating the quality of the evidence.

Step 1: Starting grade according to study design	Step 2: Lower if	Step 3: Higher if	Step 4: determine final grade for quality of evidence
Randomized trials= High Observational Studies= Low	Risk of Bias -1 Serious -2 Very Serious Inconsistency -1 Serious -2 Very Serious Indirectness -1 Serious -2 Very Serious Imprecision -1 Serious -2 Very Serious Publication Bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very Large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect when results show no effect	High (four plus: +++) Moderate (three plus: ++) Low (two plus: +) Very Low (one plus: +)

Adapted from Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, et al.

Table 7.3. Grade for the overall quality of evidence.

Grade	Quality Level	Definition
A	High	We are confident that the true effects lies close to that of the estimates of the effect
B	Moderate	The true effects are likely to be close to the estimates of the effects, but there is a possibility that they are substantially different
C	Low	The true effects might be substantially different from the estimates of effects
D	Very low	The estimates are very uncertain, and often will be far from the truth.

Adapted from Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ & GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008 336 924–926.

Formulating statements and grading recommendations

Recommendations

After the summary tables were produced and evidence profiles had been prepared, revised and approved by the guideline development group, two full-weekend plenary meetings were held in September 2012 and December 2012 to formulate and grade the recommendations.

Recommendations can be for or against a certain strategy. The guideline development group drafted the recommendations based on their interpretation of the available evidence. Judgements around four key factors determined the strength of a recommendation: the balance between desirable and undesirable consequences of alternative therapeutic or diagnostic strategies, the quality of the evidence, the variability in values and preferences. We did not conduct formal decision or cost analysis. In accordance to GRADE, we classified the strength of the recommendations as strong, coded '1' or weak, coded '2' (**Table 7.4; Figure 7.1**) [8]. Individual statements were made and discussed in an attempt to reach group consensus. If we could not reach consensus, we held a formal open vote by show of hands.

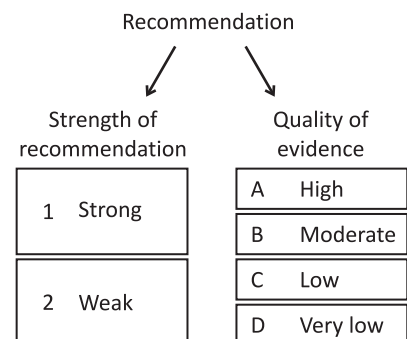
Table 7.4. Implications of strong and weak recommendations for stakeholders.

Grade	Implications		
	Patients	Clinicians	Policy
1 - STRONG 'We recommend'	Most people in your situation would want the recommended course of action, only a small proportion would not	Most patients should receive the recommended course of action	The recommendation can be adopted as a policy in most situations
2 - WEAK 'We suggest'	Most people in your situation would want the recommended course of action, but many would not	You should recognise that different choices will be appropriate for different patients You must help each patient to arrive at a management decision consistent with her or his values and preferences.	Policy making will require substantial debate and involvement of many stakeholders

Adapted from Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ & GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008 336 1049–1051. The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counselling and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements but are not meant to be interpreted as being stronger recommendations than level 1 or 2 recommendations.

Figure 7.1. Grade system for grading recommendations.

Adapted from Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ & GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008 336 924–926. [8]



An arbitrary 80% had to cast a positive vote for a statement to be accepted. Voting results and reasons for disagreement were specified in the rationale.

Ungraded statements and advice for clinical practice

We decided to use an additional category of ungraded statements for areas where formal evidence was not sought and statements were based on common sense or expert experience alone. They were termed 'statement' to differentiate them from graded recommendations and do not hold an indicator for the quality of the evidence. The ungraded statements were generally written as simple declarative statements but were not meant to be stronger than level 1 or 2 recommendations.

We also provided additional advice for clinical practice. The advice is not graded and is only for the purpose of improving practical implementation. It contains some elaboration on one of the statements, clarifying how the statement can be implemented in clinical practice.

Optimizing implementation

Recommendations often fail to reach implementation in clinical practice partly because of their wording. As part of a research project to evaluate methods for improving guideline development processes, we integrated the GuideLine Implementability Appraisal (GLIA) instrument to optimise the wording of the recommendations [9]. The tool primarily enables structured evaluation of factors such as executability (is it clear from the statement exactly what to do) and decidability (exactly under what conditions) of preliminary recommendations. In addition, the tool is designed to highlight other problems possibly hindering implementation, e.g. recommendations being inconsistent with clinicians' existing beliefs or patients' expectations. The appraisal was done by a panel of target guideline users external to the guideline development group. Comments and remarks were communicated to the guideline development group and used to help refine the recommendations.

Writing rationale

We collated recommendations and ungraded statements for each of the clinical questions in separate sections structured according to a specific format. Each question resulted in one or more specific boxed statements. Within each recommendation, the strength was indicated as level 1 or 2 and the quality of the supporting evidence as A, B, C or D as prescribed by the GRADE methodology (**Table 7.4**).

These statements are followed by advice for clinical practice where relevant and the rationale. The rationale contains a brief section on 'why this question' with relevant background and justification of the topic, followed by a short narrative review of the evidence in 'what did we find' and finally a justification of how the evidence translated in the recommendations made in 'how did we translate the evidence into the statement'.

When areas of uncertainty were identified, the guideline development group considered

making suggestions for future research based on the importance to patients or the population and on ethical and technical feasibility.

Internal and external review

Internal review

A first draft of the guideline was sent to a selected group of internal reviewers. Each society nominated experts in hyponatraemia and/or members of their governance body. Internal reviewers were asked to complete a grid-based evaluation of overall appreciation of each individual statement, using a score between 1 and 5. These scores were averaged and colour-coded between red [1] and green [5] to help visualise any problematic part. In addition, internal reviewers were asked to comment on the statements and the rationale within free text fields limited to 225 characters. All these comments and suggestions were discussed during an additional meeting of the guideline development group in June 2013. For each comment or suggestion, the guideline development group evaluated whether it was needed to adapt the statement, again taking into account the balance between desirable and undesirable consequences of the alternative management strategies, the quality of the evidence and the variability in values and preferences.

External review

The guideline was sent to the ESA and KHA–CARI for review. Reviewers could use free text to suggest amendments and/or fill in a matrix questionnaire in Microsoft Excel. In addition, all members of the ERA–EDTA received an online questionnaire with a standardised answer form in Microsoft Excel. ERA–EDTA members were asked to express to what extent they believed the individual statements were clear, implementable and to what extent they agreed with the content on a scale from 1 to 5. In addition, a free text field was provided to allow for additional comments. All these valid comments and suggestions were discussed with the guideline development group through e-mail and during a final meeting of the co-chairs of the guideline development group, the methods support team and the chair of ERBP.

Timeline and procedure for updating the guideline

It was decided to update the guideline at least every 5 years. New evidence requiring additional recommendations or changes to existing statements could instigate an earlier update.

At least every 5 years, the ERBP methods support team will update its literature searches. Relevant studies will be identified and their data will be extracted using the same procedure as for the initial guideline. During a 1-day meeting, the guideline development group will decide whether or not the original statements require updating. An updated version of the guideline will be published online accompanied by a position statement in the journals of the three societies describing the changes made.

During the 5-year interval, the guideline development group co-chairs will notify the ERBP chair of new information that may justify changes to the existing guideline. Together, they will consult at least one guideline development group member representing each of the collaborating societies. If they decide that an update is needed, an updated version of the guideline will be produced using the same procedures as for the initial guideline.

Pathophysiology of hyponatraemia

Introduction

Hyponatraemia, defined as a serum sodium concentration <135 mmol/l, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. It occurs in up to 30% of hospitalised patients and can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening [10, 11]. Because hyponatraemia can result from a varied spectrum of conditions, based on different mechanisms, we believed that it would be useful to include an introductory section that outlines some of the pathophysiological principles encountered in hyponatraemia. It was not intended to be a detailed reference section. It was only meant to clarify some of the important concepts to enhance understanding of the rationale of the statements in the guideline.

Hyponatraemia is primarily a disorder of water balance, with a relative excess of body water compared to total body sodium and potassium content. It is usually associated with a disturbance in the hormone that governs water balance, vasopressin (also called antidiuretic hormone). Even in disorders associated with (renal) sodium loss, vasopressin activity is generally required for hyponatraemia to develop. Therefore, after describing common signs and symptoms, we detail the mechanisms involved in vasopressin release.

Changes in serum osmolality are primarily determined by changes in the serum concentration of sodium and its associated anions. It is important to differentiate the concepts of total osmolality and effective osmolality or tonicity. Total osmolality is defined as the concentration of all solutes in a given weight of water (mOsm/kg), regardless of whether or not the osmoles can move across biological membranes. Effective osmolality or tonicity refers to the number of osmoles that contribute water movement between the intracellular and extracellular compartment. It is a function of the relative solute permeability properties of the membranes separating the intracellular and extracellular fluid compartments [12]. Only effective solutes create osmotic pressure gradients across cell membranes leading to osmotic movement of water between the intracellular and extracellular fluid compartment. In most cases, hyponatraemia reflects low effective osmolality or hypotonicity, which causes symptoms of cellular oedema. However, hyponatraemia may also (rarely) occur with isotonic or hypertonic serum if the serum contains many additional osmoles, such as glucose or mannitol. Therefore, we discuss not only how hypo-osmolar but also how isosmolar and hyperosmolar states develop.

Finally, we review the pathophysiology of distinct clinical disorders that can cause hy-

ponatraemia. We have categorised the causes of hyponatraemia in those associated with a reduced, normal or increased extracellular fluid volume. Although the clinical assessment of volume status is often difficult in practice, the concept of volume status has proven useful because it provides a simple framework to understand the diagnosis and treatment of hypo-osmolar disorders.

Clinical features

Symptoms can vary from mild, non-specific to severe and life-threatening (**Table 7.5**). Severe symptoms of hyponatraemia are caused by brain oedema and increased intracranial pressure. Brain cells start to swell when water moves from the extracellular to the intracellular compartment because of a difference in effective osmolality between brain and plasma. This usually occurs when hyponatraemia develops rapidly, and the brain has had too little time to adapt to its hypotonic environment. Over time, the brain reduces the number of osmotically active particles within its cells (mostly potassium and organic solutes) in an attempt to restore the brain volume (**Figure 7.2**). This process takes ~24–48 h, hence the reason for using the 48-h threshold to distinguish acute (<48 h) from chronic (\geq 48 h) hyponatraemia.

Although the more severe signs of acute hyponatraemia are well established, it is now increasingly clear that even patients with chronic hyponatraemia and no apparent symptoms can have subtle clinical abnormalities when analysed in more detail. Such abnormalities include gait disturbances, falls, concentration and cognitive deficits [13]. In addition, patients with chronic hyponatraemia more often have osteoporosis and more frequently

Table 7.5. Classification of symptoms of hyponatraemia.

Severity	Symptom
Moderately severe	Nausea without vomiting
	Confusion
	Headache
Severe	Vomiting
	Cardio-respiratory distress
	Abnormal and deep somnolence
	Seizures
	Coma (Glasgow Coma Scale \leq 8)

The guideline development group wants to underscore that these symptoms can also be induced by other conditions. Clinical and anamnestic data should be taken into account when assessing the causal relation between the hyponatraemia and a certain symptom (i.e. to assess whether the symptom has been caused by the hyponatraemia or the hyponatraemia by the underlying condition/symptom). The less pronounced (e.g. mild) the biochemical degree of hyponatraemia, the more caution should be taken when considering that the hyponatraemia is the cause of the symptoms.

This list is not exhaustive, and all symptoms that can be signs of cerebral oedema should be considered as severe or moderate symptoms that can be caused by hyponatraemia.

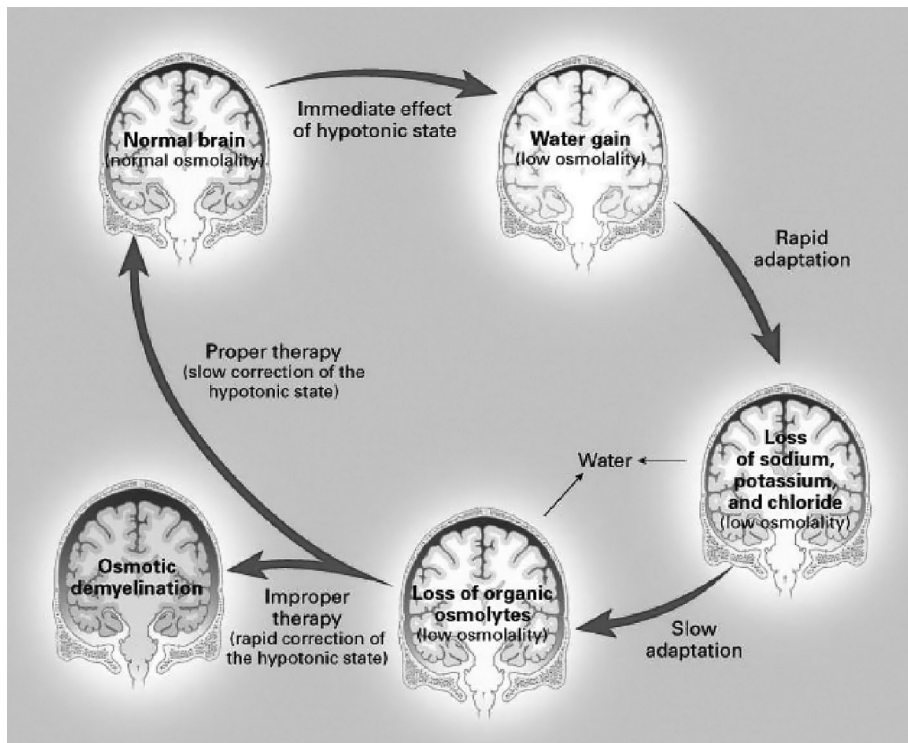


Figure 7.2. Adaptation of the brain to hypotonicity.

Reproduced with permission from Massachusetts Medical Society, Copyright © 2000 Adrogué HJ & Madias NE. Hyponatremia. *New England Journal of Medicine* 2000 342 1581–1589.

sustain bone fractures than normonatremic persons [14, 15, 16]. Finally, hyponatraemia is associated with an increased risk of death [17, 18]. Whether these are causal associations or merely symptoms of underlying problems such as heart or liver failure remains unclear [19].

Regulation of water intake and homeostasis

As the serum sodium concentration is determined by the amount of extracellular water relative to the amount of sodium, it can be regulated by changing intake or output of water. The major mechanisms responsible for regulating water metabolism are thirst and the pituitary secretion and renal effects of vasopressin. Regulation of body water serves to minimise osmotically induced disruptions in cell volume with adverse effects on multiple cellular functions. Osmoreceptive neurons located in the anterior hypothalamus detect changes in cell stretch due to changes in systemic effective osmolality. A decrease in cell stretch increases the firing rate of osmoreceptive neurons, which leads to both increased thirst and increased release of vasopressin from the pituitary gland. Vasopressin in turn increases the re-absorption of water from the primitive urine in the distal tubules of the nephron, which leads to urine that is more concentrated. To prevent persistent thirst, the threshold for re-

leasing vasopressin is lower than that for triggering thirst (**Figure 7.3**) [12].

Osmoregulation and vasopressin release

Under normal circumstances, osmotic regulation of the release of vasopressin from the posterior pituitary primarily depends on the effective osmolality of the serum. Central osmoreceptors, expressing transient receptor potential vanilloid 1 (TRPV1), and peripheral osmoreceptors, expressing TRPV4, relay the information on osmolality [20, 21]. The stretch-inactivating cationic TRPV1 and TRPV4 channels transduce osmotically evoked changes in cell volume into functionally relevant changes in membrane potential. TRPV1 is an osmotically activated channel expressed in the vasopressin producing magnocellular cells and in the circumventricular organs [22, 23]. Recently, afferent neurons expressing the osmotically activated ion channel TRPV4 (able to detect physiological hypo-osmotic shifts in blood osmolality) have been identified in the thoracic dorsal root ganglia, which innervate hepatic blood vessels [21].

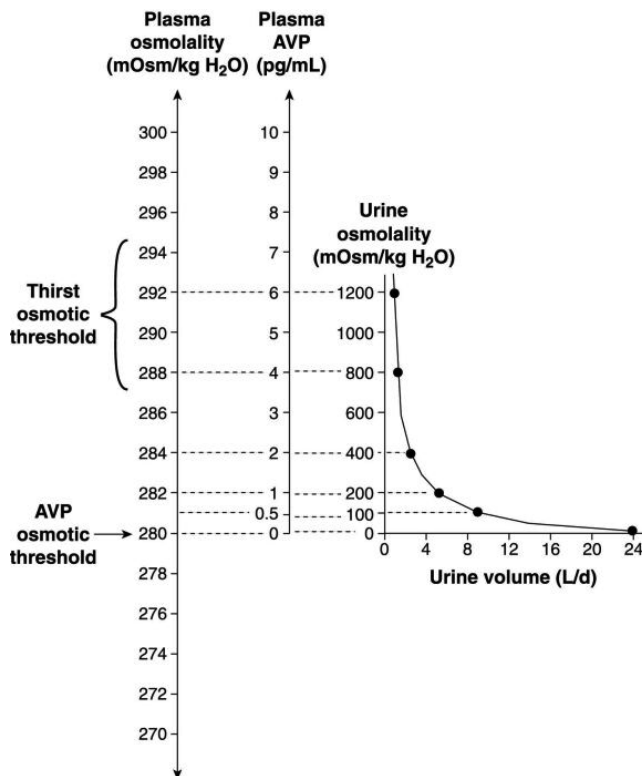


Figure 7.3. Osmotic stimulation of vasopressin release.

Schematic representation of normal physiological relationships among plasma osmolality, plasma AVP concentrations, urine osmolality and urine volume in man. Note particularly the inverse nature of the relationship between urine osmolality and urine volume, resulting in disproportionate effects of small changes in plasma AVP concentrations on urine volume at lower AVP levels. Reproduced with permission from Elsevier Copyright © 2003 Verbalis JG. Disorders of body water homeostasis. Best Practice & Research. Clinical Endocrinology & Metabolism 2003 17 471–503.

Baroregulation of vasopressin release

Stretch-sensitive receptors in the left atrium, carotid sinus and aortic arch sense circulating volume. When the circulating volume is increased, afferent neural impulses inhibit the secretion of vasopressin [12]. Conversely, when the volume is decreased, the discharge rate of the stretch receptors slows and vasopressin secretion increases [24]. Reductions in blood pressure as little as 5% increase the serum vasopressin concentration [25]. In addition, there seems to be an exponential association between the serum vasopressin concentration and the percentage decline in mean arterial blood pressure, with faster increases as blood pressure progressively decreases.

Because osmoregulated and baroregulated vasopressin secretion are interdependent, renal water excretion can be maintained around a lower set point of osmolality under conditions of moderately decreased circulating volume [26]. As the circulatory hypovolaemia worsens, the serum vasopressin concentration dramatically increases and baroregulation overrides the osmoregulatory system.

Osmosensitive neurons are located in the subfornical organ and the organum vasculosum of the lamina terminalis. Because these neurons lie outside the blood–brain barrier, they integrate osmotic information with endocrine signals borne by circulating hormones, such as angiotensin II and atrial natriuretic peptide. The direct angiotensin II effect on osmoregulatory neurons has been termed ‘osmoregulatory gain’ since Zhang *et al.* [27] have shown that in rats, angiotensin II amplifies osmosensory transduction by enhancing the proportional relationship between osmolality, receptor potential and action potential firing in supra-optic nucleus neurons. Modifications in osmoregulatory gain induced by angiotensin, together with changes in vasopressin secretion induced by baroregulation (see below), may explain why the changes in the slope and threshold of the relationship between serum osmolality and vasopressin secretion are potentiated by hypovolaemia or hypotension and are attenuated by hypervolaemia or hypertension (**Figure 7.4**) [28].

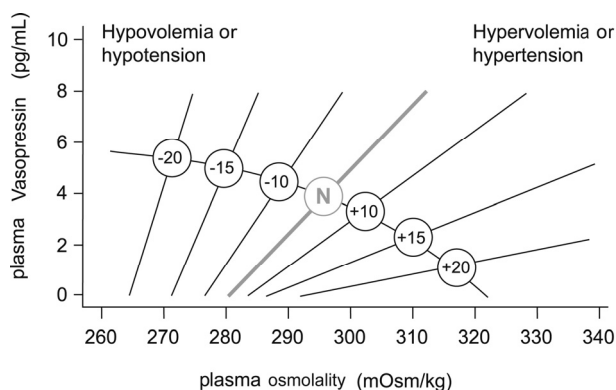


Figure 7.4. Effects of hypovolaemia on osmoreceptor gain.

Reproduced with permission from The Endocrine Society Copyright © 1976 Robertson GL & Athar S. The interaction of blood osmolality and blood volume in regulating plasma vasopressin in man. *Journal of Clinical Endocrinology and Metabolism* 1976 42 613–620.

Unregulated vasopressin release

The posterior pituitary is the only organ in which regulated vasopressin release takes place. Under pathological conditions, both pituitary and other cells may also synthesise and secrete vasopressin independent of serum osmolality or circulating volume. Originally, Schwartz & Bartter [29] introduced the term syndrome of inappropriate antidiuretic hormone secretion (SIADH) as an overarching term. We now know that both genetic and pharmacological factors can also increase water permeability in the collecting duct in the absence of vasopressin. Others have previously introduced the term syndrome of inappropriate antidiuresis (SIAD) to cover both situations. We will use it throughout this text.

Renal actions of vasopressin

In order to re-absorb water from the collecting duct, and to concentrate the urine, the collecting duct must become permeable to water. The basolateral membrane is always permeable to water because of aquaporin-3 and aquaporin-4 water channels. Vasopressin regulates the permeability of the apical membrane by insertion of aquaporin-2 water channels through vasopressin-2-receptor activation. The high osmolality of the medulla provides the driving force needed for re-absorption of water from the collecting duct. Thanks to the counter current configuration of the loops of Henle, the kidney is able to create solute gradients from the cortex to the inner medulla. Because of the re-absorption of both sodium and urea from the lumen, the osmolality of the tip of the medulla may reach 1200 mOsm/l in case of water depletion. The medullary osmolality determines maximum urine osmolality and is influenced by vasopressin.

Pseudohyponatraemia

Pseudohyponatraemia is a laboratory artefact that occurs when abnormally high concentrations of lipids or proteins in the blood interfere with the accurate measurement of sodium. Pseudohyponatraemia was seen more frequently with flame photometric measurement of serum sodium concentration than it is now with ion-selective electrodes, but despite common opinion to the contrary, it still occurs [30], because all venous blood samples are diluted and a constant distribution between water and the solid phase of serum is assumed when the serum sodium concentration is calculated [30] (**Figure 7.5**). Serum osmolality is measured in an undiluted sample and the result will be within the normal range in case of pseudohyponatraemia. If the measurement of serum osmolality is not available, direct potentiometry using a blood gas analyser will yield the true sodium concentration, as this measures the sodium concentration in an undiluted sample too.

Reset osmostat

In reset osmostat, there is a change in the set point as well as in the slope of the osmoregulation curve [12]. The response to changes in osmolality remains intact. We see this phenomenon, for example, in pregnancy where the serum sodium concentration may mildly

decrease 4–5 mmol/l.

Non-hypotonic hyponatraemia

Isotonic hyponatraemia

In the majority of patients that present with hyponatraemia, the serum is hypotonic, i.e. both the sodium concentration and the effective osmolality are low. Sometimes, the serum contains additional osmoles that increase effective osmolality and reduce the serum sodium concentration by attracting water from the intracellular compartment. Examples of such osmoles include glucose (hyperglycaemia due to uncontrolled diabetes mellitus), mannitol and glycine (absorption of irrigation fluids during urological or gynaecological surgery) [31, 32, 33]. The resulting 'translocational' hyponatraemia is often wrongly considered a form of pseudohyponatraemia. However, as described earlier, in pseudohyponatraemia, serum osmolality is normal and no shifts of water occur.

Hypertonic hyponatraemia

In hyperglycaemia-induced hyponatraemia, hyponatraemia is caused by dilution due to hyperosmolality. It is important to make the distinction between measured osmolality and effective osmolality [34].

Effective osmolality may be calculated with the following equations:

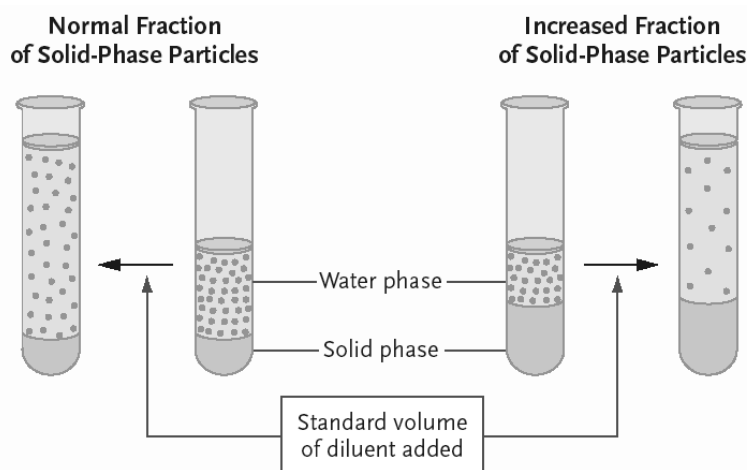


Figure 7.5. Pseudohyponatraemia.

Normally, serum contains 7% solids by volume. In order to reduce the volume of blood needed for analysis, serum is frequently diluted before the actual measurement is obtained. The same volume of diluent is always used; the degree of dilution is estimated under the assumption that the serum contains 7% solid-phase particles. When the fraction of solid-phase particles is increased, the same amount of diluent results in a greater dilution, unbeknownst to the laboratory personnel (right side of figure). Consequently, the calculation of an ion level with the use of a degree of dilution that is based on the incorrect fraction of solid-phase particles will lead to an underestimate. Reproduced with permission from Massachusetts Medical Society Copyright © 2003 Turchin A, Seifter JL & Seely EW. Clinical problem-solving. Mind the gap. New England Journal of Medicine 2003 349 1465–1469.

- Effective osmolality (mmol/kg H₂O) =
 $2 \times (\text{serum Na (mmol/l)} + \text{serum K (mmol/l)}) + \text{serum glycaemia (mg/dl)}/18$
- Effective osmolality (mmol/kg H₂O) =
 $2 \times (\text{serum Na (mmol/l)} + \text{serum K (mmol/l)}) + \text{serum glycaemia (mmol/l)}$

This includes only osmoles that are restricted to the extracellular fluid volume. As water returns to the intracellular space during treatment of hyperglycaemia, serum sodium concentration should increase, thus resulting in a constant effective osmolality. If it does not, brain oedema may ensue due to an overly rapid drop in effective osmolality [35].

Ineffective osmoles

High urea concentrations in kidney disease may also increase measured osmolality. However, urea is not an effective osmole because it readily passes across the cellular membrane. It does not change effective osmolality, does not attract water to the extracellular fluid compartment and does not cause hyponatraemia [36].

Hypotonic hyponatraemia with decreased extracellular fluid volume

Depletion of circulating volume, with or without deficit of total body sodium, can markedly increase the secretion of vasopressin leading to water retention despite hypotonicity. Although the vasopressin release in this case is inappropriate from an osmoregulatory point of view, it happens in order to preserve intravascular volume and can be considered appropriate from a circulatory point of view.

Non-renal sodium loss

Gastrointestinal sodium loss

Volume depletion can occur if the body loses sodium through its gastrointestinal tract. In case of severe diarrhoea, the kidneys respond by preserving sodium and urine sodium concentrations are very low. In case of vomiting, metabolic alkalosis causes renal sodium loss as sodium accompanies bicarbonate in the urine despite activation of the renin–angiotensin system. By contrast, in patients with diarrhoea, chloride accompanies ammonium excreted by the kidneys in an effort to prevent metabolic acidosis.

Transdermal sodium loss

The body can lose substantial amounts of sodium transdermally due to heavy sweating. This may be caused by impaired re-absorption of sodium in the sweat duct as in cystic fibrosis or by an impaired natural barrier function due to extensive skin burns. It results in increased vulnerability to sodium depletion and volume depletion. The amount of sodium that is lost in sweat varies markedly between healthy individuals, but to date, no link has been found between the sodium concentration in sweat and cystic fibrosis-causing mutations of the cystic fibrosis transmembrane conductance regulator gene [37].

Renal sodium loss

Diuretics

Urinary sodium loss can cause volume depletion and, if sufficiently severe, trigger vasopressin release. Diuretics and especially thiazides are frequently implicated as a cause of hyponatraemia. The traditional explanation is that renal sodium loss leads to volume contraction with subsequent release of vasopressin. However, this would require a substantial loss of sodium and body weight, while patients with thiazide-induced hyponatraemia often have increased body weight [38]. It might be reasonable to assume that thiazides directly induce the release of vasopressin or increase the response of the collecting duct to circulatory vasopressin. In any case, there appears to be an individual susceptibility to these effects, as hyponatraemia only occurs in certain patients and usually reoccurs if thiazides are reintroduced [38]. Despite the potential for causing more urinary sodium loss, loop diuretics only rarely cause hyponatraemia because they reduce osmolality in the renal medulla and thus limit the kidney's ability to concentrate urine [39].

Primary adrenal insufficiency

In primary adrenal insufficiency, hypoaldosteronism causes renal sodium loss, contracted extracellular fluid volume and hyponatraemia. Although primary adrenal insufficiency usually presents in combination with other clinical symptoms and biochemical abnormalities, hyponatraemia can be its first and only sign [40].

Cerebral salt wasting

Renal sodium loss has been documented in patients with intracranial disorders such as subarachnoid bleeding. This renal salt wasting has been rather confusingly named 'cerebral' salt wasting, and increased levels of brain natriuretic peptide have been implicated in its pathogenesis [41]. Because diagnosis may be difficult, and both inappropriate antidiuresis and secondary adrenal insufficiency are actually more common in this clinical setting, cerebral salt wasting may be over diagnosed [42]. Nevertheless, the recognition of cerebral salt wasting is important because its treatment requires volume resuscitation rather than water restriction.

Kidney disease

Renal salt wasting can also occur in kidney dysfunction. The so-called salt-losing nephropathies, such as tubulopathy after chemotherapy or in analgesic nephropathy, medullary cystic kidney disease and certain pharmacological compounds can inhibit the kidney's ability to re-absorb appropriate amounts of sodium [43].

Third spacing

Bowel obstruction, pancreatitis, sepsis or muscle trauma may markedly reduce effective circulating blood volume through fluid leakage from blood vessels. This causes baroreceptor activation and vasopressin release, which may result in hyponatraemia. Infusion of hypotonic fluids in this case may worsen hyponatraemia.

Hypotonic hyponatraemia with normal extracellular fluid volume

Euvolaemic hyponatraemia is caused by an absolute increase in body water, which results from an excessive fluid intake in the presence of an impaired free water excretion, either due to inappropriate release of vasopressin or due to a low intake of solutes.

Syndrome of inappropriate antidiuresis

The vasopressin secretion in SIADH is inappropriate because it occurs independently from effective serum osmolality or circulating volume. It may result from increased release by the pituitary gland or from ectopic production. Inappropriate antidiuresis may also result from increased activity of vasopressin in the collecting duct or from a gain-of-function mutation in its type 2 receptor [44]. Throughout this text, we will use the terminology 'SIAD' as an overarching term because management principles are the same for both conditions and any distinction is merely academic and out of the scope of this document [45].

In SIAD, antidiuresis causes progressive hyponatraemia until the expression of vasopressin V2 receptors and aquaporin-2 water channels is down-regulated, a process appropriately called 'vasopressin escape' [46]. Because of the vasopressin activity, urine osmolality will be inappropriately high (usually >100 mOsm/l) and this is one of the criteria required for a diagnosis of SIAD. The criteria are largely the same as originally proposed by Bartter & Schwartz [29]. Importantly, SIAD remains a diagnosis of exclusion (**Table 7.6**).

General anaesthesia, nausea, pain, stress and a variety of drugs are non-specific but potent stimuli for the secretion of vasopressin and a frequent cause of SIAD in hospitalised patients. The use of prescribed or illicit drugs may result in either increased vasopressin release or increased effects of vasopressin in the collecting duct. The most frequent causes of increased inappropriate secretion of vasopressin include cancers (e.g. small cell carcinoma

Table 7.6. *Diagnostic criteria for the syndrome of inappropriate antidiuresis.*

Essential criteria
Effective serum osmolality < 275 mOsm/kg
Urine osmolality > 100 mOsm/kg at some level of decreased effective osmolality
Clinical euvolaemia
Urine sodium concentration > 30 mmol/L with normal dietary salt and water intake
Absence of adrenal, thyroid, pituitary or renal insufficiency
No recent use of diuretic agents
Supplemental criteria
Serum uric acid < 0.24 mmol/L (< 4 mg/dL)
Serum urea < 3.6 mmol/L (< 21.6 mg/dL)
Failure to correct hyponatraemia after 0.9% saline infusion
Fractional sodium excretion $> 0.5\%$
Fractional urea excretion $> 55\%$
Fractional uric acid excretion $> 12\%$
Correction of hyponatraemia through fluid restriction

Adapted from Schwartz WB, Bennett W, Curelop S & Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *American Journal of Medicine* 1957 23 529–542 [29] and Janicic N & Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinology and Metabolism Clinics of North America* 2003 32 459–481, vii.

of the lung) and diseases of the lung (e.g. pneumonia) or central nervous system (e.g. subarachnoid haemorrhage) (**Table 7.7**). Recently, several genetic disorders causing SIAD have

Table 7.7. Causes of the syndrome of inappropriate antidiuresis.

Malignant diseases	Pulmonary disorders	Disorders of the nervous system	Drugs	Other causes
Carcinoma Lung Oropharynx Gastro-intestinal tract stomach duodenum pancreas Genitourinary tract ureter bladder prostate endometrium Endocrine thymoma Lymphomas Sarcomas Ewing's sarcoma Olfactory neuroblastoma	Infections Bacterial pneumonia Viral pneumonia Pulmonary abscess Tuberculosis Aspergillosis Asthma Cystic fibrosis Respiratory failure associated with positive-pressure breathing	Infection Encephalitis Meningitis Brain abscess Rocky Mountain spotted fever AIDS Malaria Vascular and masses Subdural hematoma Subarachnoid haemorrhage Stroke Brain tumours Head trauma Other Hydrocephalus Cavernous sinus thrombosis Multiple sclerosis Guillain-Barré syndrome Shy-Drager syndrome Delirium tremens Acute intermittent porphyria	Vasopressin release or action stimulants Antidepressants - SSRIs - Tricyclic - MAOI - Venlafaxine Anticonvulsants - Carbamazepine - Oxacarbamazepine - Sodium valproate - Lamotrigine Antipsychotics - Phenothiazides - Butyrophenones Anticancer drugs - Vinca alkaloids - Platinum compounds - Ifosfamide - Melphalan - Cyclophosphamide - Methotrexate - Pentostatin Antidiabetic drugs - Chlorpropamide - Tolbutamide Miscellaneous - Opiates - MDMA (XTC) - Levamisole - Interferon - NSAIDs - Clofibrate - Nicotine - Amiodarone - Proton pump inhibitors - Monoclonal antibodies Vasopressin analogues Desmopressin Oxytocin Terlipressin Vasopressin	Hereditary Gain-of-function mutation of the vasopressin V ₂ receptor Idiopathic Transient Exercise-associated hyponatraemia General anesthesia Nausea Pain Stress

Adapted from Liamis G al. *Am J Kidney Dis* 2008; 52: 144-153.

AIDS, acquired immunodeficiency syndrome; MOAI, monoamine oxidase inhibitors; MDMA, 3, 4-methylenedioxymethamphetamine; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

been identified. Among them are polymorphisms resulting in a loss-of-function of *TRPV4*, a gene that encodes for an osmosensitive calcium channel expressed in osmosensing neurons [47]. Another is a gain-of-function mutation in the vasopressin 2 receptor, resulting in a constitutively activated receptor causing increased water re-absorption and chronic hyponatraemia [44].

Secondary adrenal insufficiency

The production of aldosterone is less impaired in secondary than in primary adrenal insufficiency and renal sodium loss does not contribute to the development of hyponatraemia. Secondary adrenal insufficiency is caused by reduced or absent secretion of adrenocorticotrophic hormone, resulting in hypocortisolism. Under normal circumstances, cortisol suppresses both production of corticotrophin-releasing hormone and vasopressin in the hypothalamus. In secondary adrenal insufficiency, persistently low concentrations of cortisol fail to suppress vasopressin and hyponatraemia results from impaired free water excretion, as it does in SIAD [48].

Hypothyroidism

Although included in many diagnostic algorithms, hypothyroidism very rarely causes hyponatraemia [49]. In 2006, Warner *et al.* [50] observed that serum sodium concentration decreased by 0.14 mmol/l for every 10 mU/l rise in thyroid-stimulating hormone, indicating that only severe cases of clinically manifest hypothyroidism resulted in clinically important hyponatraemia. Development of hyponatraemia may be related to myxoedema, resulting from a reduction in cardiac output and glomerular filtration rate [51].

High water and low solute intake

Under conditions of high water and low solute intake, the excess water intake is primarily responsible for hyponatraemia. Vasopressin activity is absent, which is reflected by an appropriately low urine osmolality, usually <100 mOsm/kg. Patients with primary polydipsia drink more than what the kidneys can eliminate. Primary polydipsia may occur in combination with psychiatric disorders such as schizophrenia. Although excess water intake contributes most to hyponatraemia, renal loss of solutes and an acquired impairment in free water excretion may also occur [52].

The amount of water that the kidneys can remove on a daily basis depends on solute excretion and hence solute intake. Depending on the kidney's ability to dilute urine, 50–100 mmol of solutes, such as urea and salts, are required to remove 1 l of fluid. If solute intake is low relative to water intake, the number of available osmoles can be insufficient to remove the amount of water ingested. This is seen in patients with anorexia (nervosa), beer potomania and so-called 'tea and toast' hyponatraemia [53].

Hypotonic hyponatraemia with increased extracellular fluid volume

Kidney disease

When glomerular filtration rate deteriorates, or when there is tubular injury or scarring, the ability to dilute urine and excrete free water decreases. In advanced kidney disease, urine osmolality is usually close to serum osmolality (isosthenuria). Free water removal is no longer regulated by vasopressin but is determined by the number of osmoles excreted in the urine (i.e. solute intake). Consequently, hyponatraemia can readily develop if patients do not adhere to fluid restriction. In addition, in patients treated with peritoneal dialysis, the use of icodextrin-based dialysis solutions can cause clinically relevant hyponatraemia [54].

Heart failure

Approximately 20–30% of patients with chronic heart failure New York Heart Association (NYHA) classes III and IV have hyponatraemia [55]. It is associated with more severe heart failure and an increased risk of death, independent of other comorbid conditions [55, 56]. Whether this reflects (unacknowledged) disease severity or has a causal effect remains unclear. Although renal sodium retention tends to increase the extracellular volume, the effective circulating blood volume is generally reduced due to impaired cardiac output. Baroreceptor-mediated neurohumoral activation commonly results in increased secretion of vasopressin by the pituitary. Simultaneous activation of the renin–angiotensin system and increased release of vasopressin reduces urinary sodium excretion and increases urine osmolality. Although simultaneous use of diuretics may contribute to the development of hyponatraemia, loop diuretics have less potential for causing hyponatraemia than thiazides.

Liver failure

Also in liver failure, hyponatraemia is associated with poorer survival [57]. Whether this reflects disease severity or has a direct contributory effect remains unclear [58]. Systemic vasodilation and arteriovenous shunting of blood may reduce the effective arterial blood volume. As in heart failure, this reduction can lead to neurohumoral activation and water retention due to baroreceptor-mediated vasopressin release.

In addition, mineralocorticoid receptor blockers such as spironolactone, which either alone or in combination with loop diuretics, are frequently used to reduce sodium retention in liver failure, can contribute to hyponatraemia [59].

Nephrotic syndrome

In nephrotic syndrome, blood volume may be decreased due to the lower serum oncotic pressure (under-fill hypothesis). If this happens, stimulation of vasopressin secretion can cause patients to develop hyponatraemia. The tendency for water retention is generally balanced by intense sodium retention, but the increased renal re-absorption of sodium usually necessitates a considerable dose of diuretics. The combination of increased vasopressin

release and diuretic use may promote moderate hyponatraemia, especially in children with low blood pressure [60].

Diagnosis of hyponatraemia

Classification of hyponatraemia

Definition of hyponatraemia based on biochemical severity

- We define 'mild' hyponatraemia as a biochemical finding of a serum sodium concentration between 130 and 135 mmol/l as measured by ion-specific electrode.
- We define 'moderate' hyponatraemia as a biochemical finding of a serum sodium concentration between 125 and 129 mmol/l as measured by ion-specific electrode.
- We define 'profound' hyponatraemia as a biochemical finding of a serum sodium concentration <125 mmol/l as measured by ion-specific electrode.

Definition of hyponatraemia based on time of development

- We define 'acute' hyponatraemia as hyponatraemia that is documented to exist <48 h.
- We define 'chronic' hyponatraemia as hyponatraemia that is documented to exist for at least 48 h.
- If hyponatraemia cannot be classified, we consider it being chronic, unless there is clinical or anamnestic evidence of the contrary (**Table 7.8**).

Definition of hyponatraemia based on symptoms

- We define 'moderately symptomatic' hyponatraemia as any biochemical degree of hyponatraemia in the presence of moderately severe symptoms of hyponatraemia (**Table 7.5**).

Table 7.8. *Drugs and conditions associated with acute hyponatraemia (< 48 hours)*

Postoperative phase
Post-resection of the prostate, post-resection of endoscopic uterine surgery
Polydipsia
Exercise
Recent thiazides prescription
3,4-methyleendioxyamphetamine (MDMA, XTC)
Colonoscopy preparation
Cyclophosphamide (intravenous)
Oxytocin
Recently started desmopressin therapy
Recently started terlipressin, vasopressin

- We define ‘severely symptomatic’ hyponatraemia as any biochemical degree of hyponatraemia in the presence of severe symptoms of hyponatraemia (**Table 7. 5**).

Rationale

Why did we choose to set definitions?

Hyponatraemia can be classified based on different parameters. These include serum sodium concentration, rate of development, symptom severity, serum osmolality and volume status. For this guideline, we wanted the classification to be consistent and clear so that all users would have a correct understanding of the terminology used. We also wanted to make the classification directly relevant for patient management. However, treatment strategies cannot be adequately classified with reference to a single criterion. Hence, treatment strategies have been classified according to combinations of these criteria.

What are these definitions based on?

Classification based on serum sodium concentration

Authors mostly use the terms ‘mild’, ‘moderate’ and ‘severe’ [61, 62,63]. We have chosen to replace ‘severe’ by ‘profound’ to avoid confusion with the classification based on symptoms, for which we have reserved the term ‘severe’. The definitions of mild, moderate and profound hyponatraemia in published research are variable, especially the threshold used to define profound hyponatraemia for which values have ranged from 110 to 125 mmol/l [64, 65]. Several studies report that when serum sodium concentrations drop below 125 mmol/l, symptoms become more common [61, 66, 67, 68, 69, 70, 71], and the correction to normonatraemia necessitates careful monitoring to avoid overly rapid correction [72].

Classification based on duration and speed of development

Published research suggests using a threshold of 48 h to distinguish ‘acute’ from ‘chronic’ hyponatraemia. Brain oedema seems to occur more frequently when hyponatraemia develops in <48 h [73, 74, 75,76]. Experimental studies also suggest that the brain needs 48 h to adapt to a hypotonic environment, achieved mainly by extruding sodium, potassium, chloride and organic osmoles from its cells [77, 78,79]. Before adaptation, there is a risk of brain oedema because the lower extracellular osmolality promotes a shift of water into the cells. However, once adaptation is completed, brain cells can again sustain damage if the serum sodium concentration increases too rapidly. Breakdown of the myelin sheath insulating individual neurons can result in what is called the osmotic demyelination syndrome [80, 81,82, 83]. Consequently, it is important to distinguish between acute and chronic hyponatraemia to assess whether someone is at a greater risk of immediate brain oedema than of osmotic demyelination [84]. Unfortunately, in clinical practice, the distinction between acute and chronic hyponatraemia is often unclear, particularly for patients presenting to the emergency room. It is often unknown when the serum sodium concentration has started decreasing. If classifying hyponatraemia as acute or chronic is not possible, we have decided to consider hyponatraemia as being chronic, unless there are reasons to assume

it is acute (Table 7.8). There is a good reason for this approach. Chronic hyponatraemia is much more common than acute hyponatraemia and should be managed accordingly to avoid osmotic demyelination [85, 86].

Classification based on symptoms

We have divided symptoms of hyponatraemia into 'moderately severe' and 'severe'. The distinction is based on selected observations in acute hyponatraemia; those who subsequently die more often experience what we define as severe symptoms than those who live [73, 74]. Moderately severe symptoms caused by brain oedema are less frequently associated with death. Nevertheless, they may rapidly progress to more severe symptoms associated with an adverse outcome.

We have purposefully omitted the category 'asymptomatic' as we believed this might create confusion. Patients are probably never truly 'asymptomatic' in the strictest sense of the word. Very limited and subclinical signs such as mild concentration deficits are seen even with mild hyponatraemia [13].

A classification based on symptoms aims to reflect the degree of brain oedema and the extent of immediate danger. It allows matching treatment to the immediate risk, with more aggressive treatment for symptoms that are more severe. Nevertheless, a classification based only on symptom severity has several shortcomings. First, symptoms of acute and chronic hyponatraemia may overlap [18]. Secondly, patients with acute hyponatraemia can present without clear symptoms, but go on to develop moderately severe to severe symptoms within hours [73]. Thirdly, symptoms of hyponatraemia are non-specific. Consequently, assessment of symptoms needs to happen with caution. Clinicians need to be wary that symptoms can be caused by conditions other than hyponatraemia, by other conditions in combination with hyponatraemia or by conditions that cause hyponatraemia. In general, one should be particularly careful when attributing moderately severe to severe symptoms to hyponatraemia when the biochemical degree of hyponatraemia is only mild (**Table 7.5**).

Classification based on serum osmolality

As this guideline aimed to cover the aspects of diagnosis and treatment specifically of hypotonic hyponatraemia, we needed to define what distinguishes hypotonic from non-hypotonic hyponatraemia. Because this distinction is a necessary first step in the diagnostic evaluation of any hyponatraemia, we have devoted a separate section to this topic (section 6.2). For reasons of completeness, we briefly mention it here. A measured serum osmolality <275 mOsm/kg always indicates hypotonic hyponatraemia, as effective osmolality can never be higher than total or measured osmolality. By contrast, if calculated osmolality is <275 mOsm/kg, hyponatraemia can be hypotonic, isotonic or hypertonic, depending on which osmotically active agents are present and whether or not they are incorporated in the formula.

Classification based on volume status

Patients with hyponatraemia may be hypovolaemic, euvolaemic or hypervolaemic [87].

Many traditional diagnostic algorithms start with a clinical assessment of volume status [88]. However, it is often not clear whether volume status in this context refers to the extracellular fluid volume, to the effective circulating volume or to the total body water. In addition, the sensitivity and specificity of clinical assessments of volume status are low, potentially leading to misclassification early in the diagnostic tree [89, 90]. Therefore, we have used the terms 'effective circulating volume' and 'extracellular fluid volume' throughout the text to reduce ambiguity.

Note of caution

We wanted the classification of hyponatraemia to be consistent, easy to use and helpful for both differential diagnosis and treatment. Hyponatraemia can be classified according to different factors, each with advantages and pitfalls depending on the clinical setting and situation. We have prioritised the criteria such that we would obtain a classification that would be clinically relevant and as widely applicable as possible.

Nevertheless, the user should keep in mind that differential diagnosis of hyponatraemia is difficult and no classification can be 100% accurate in every situation. We emphasise that the different classifications of hyponatraemia are not mutually exclusive and that classification should always occur with the clinical condition and the possibility of combined causes of hyponatraemia in mind.

Questions for future research

- Is it possible to define thresholds of serum sodium concentration that categorise separate entities in terms of management and outcomes?
- Is 48 h the best threshold to separate acute from chronic hyponatraemia?
- Is it possible to identify symptoms or parameters that can reliably differentiate acute from chronic hyponatraemia?

Confirming hypotonic and excluding non-hypotonic hyponatraemia

- We recommend excluding hyperglycaemic hyponatraemia by measuring the serum glucose concentration and correcting the measured serum sodium concentration for the serum glucose concentration if the latter is increased (1D).
- Hyponatraemia with a measured osmolality <275 mOsm/kg always reflects hypotonic hyponatraemia (not graded).
- Accept as 'hypotonic hyponatraemia' a hyponatraemia without evidence for causes of non-hypotonic hyponatraemia as listed in Table 7.10 (not graded).

Advice for clinical practice

Estimates of the serum sodium concentration corrected for the presence of hyperglycaemia can be obtained from the following equations [31]:

$$\text{Corrected serum [Na}^+]= \text{measured [Na}^+] + 2.4 * \frac{[\text{Glucose (mg/dL)} - 100 \text{ mg/dL}]}{100 \text{ mg/dL}}$$

$$\text{Corrected serum [Na}^+]= \text{measured [Na}^+] + 2.4 * \frac{[\text{Glucose (mmol/L)} - 5.5 \text{ mmol/L}]}{5.5 \text{ mmol/L}}$$

Na⁺, serum sodium concentration; glucose, serum glucose concentration.

This translates into adding 2.4 mmol/l to the measured serum sodium concentration for every 5.5 mmol/l (100 mg/dl) incremental rise in serum glucose concentration above a standard serum glucose concentration of 5.5 mmol/l (100 mg/dl).

Alternatively, the estimated value of the corrected serum sodium concentration across a range of serum glucose concentrations can be obtained from **Table 7.9**.

Rationale

- Why the question?

Non-hypotonic hyponatraemia does not cause brain oedema and is managed differently from hypotonic hyponatraemia. As this guideline covers management of hypotonic hyponatraemia, confirmation of hypotonicity is a prerequisite.

Table 7.9. Association between serum glucose concentration, measured serum sodium, and corrected serum sodium concentration.

Measured [Na ⁺] (mmol/L)	Measured [Glucose] (mg/dL)							
	100	200	300	400	500	600	700	800
True [Na ⁺] (mmol/L)								
135	135	137	140	142	145	147	149	152
130	130	132	135	137	140	142	144	147
125	125	127	130	132	135	137	139	142
120	120	122	125	127	130	132	134	137
115	115	117	120	122	125	127	129	132
110	110	112	115	117	120	122	124	127
105	105	107	110	112	115	117	119	122
100	100	102	105	107	110	112	114	117
95	95	97	100	102	105	107	109	112
90	90	92	95	97	100	102	104	107
85	85	87	90	92	95	97	99	102
80	80	82	85	87	90	92	94	97
75	75	77	80	82	85	87	89	92
70	70	72	75	77	80	82	84	87

Calculated using equation from Hillier TA et al. Am J Med 1999; 106: 399-403.

- What are the criteria based on?

There are broadly three categories of non-hypotonic hyponatraemia: hyponatraemia in the presence of a surplus of 'effective' osmoles, hyponatraemia in the presence of a surplus of 'ineffective' osmoles and pseudohyponatraemia (**Table 7.10**) [30, 34, 36, 88, 91].

Effective osmoles

Exogenous or endogenous solutes to which cell membranes are impermeable are restricted to the extracellular fluid compartment and are effective osmoles because they create osmotic pressure gradients across cell membranes leading to osmotic movement of water from the intracellular to the extracellular compartment [34, 36]. Because dilutional hyponatraemia results from the water shift from the intracellular to the extracellular compartment, there is no risk of brain oedema. Depending on the serum concentration of effective osmoles, the resulting non-hypotonic hyponatraemia can be isotonic or hypertonic. The prime example is hyperglycaemia [31]. Others include infusion of mannitol or perioperative absorption of irrigation fluids such as glycine [32, 33]. The latter most frequently occurs during transurethral resection of the prostate (TURP) and is therefore also referred to as 'TURP-syndrome'. Although TURP syndrome causes isotonic hyponatraemia and hence does not cause brain oedema, neurological symptoms may develop due to accumulation of ammonia, serine or glyoxylate from the metabolism of glycine [92, 93].

It is important to understand the kinetics of non-hypotonic hyponatraemia in the presence of effective osmoles. When glucose, mannitol or glycine are metabolised or excreted, serum osmolality decreases. This reduces the osmotic gradient, resulting in less water being pulled from the cells and spontaneously limiting the degree of hyponatraemia. It explains why during treatment of diabetic ketoacidosis or the hyperosmolar hyperglycaemic state a

Table 7.10. Causes of non-hypotonic hyponatraemia.

Setting	Serum osmolality	Examples
Presence of "effective" osmoles that raise serum osmolality and can cause hyponatraemia	Isotonic or hypertonic	Glucose [31] Mannitol [32] Glycine [33] Histidine-tryptophane-ketoglutarate [245] Hyperosmolar radiocontrast media [246] Maltose [247]
Presence of "ineffective" osmoles that raise serum osmolality <u>but do not</u> cause hyponatraemia	Isotonic or hyperosmolar	Urea[36] Alcohols [36] Ethylene-glycol [36]
Presence of endogenous solutes that cause pseudohyponatraemia (laboratory artifact)	Isotonic	Triglycerides [99] , cholesterol [99], protein Intravenous immunoglobulins [98] Monoclonal gammopathies [248]

decrease in serum glycaemia leads to a 'spontaneous' rise in the serum sodium concentration. If the serum glucose concentration drops to a greater extent than the serum sodium concentration rises, serum effective osmolality will decrease. This can lead to brain oedema [35, 94]. Consequently, calculating 'effective' osmolality during treatment is important [35].

Ineffective osmoles

Solutes to which cell membranes are permeable are ineffective solutes because they do not create osmotic pressure gradients across cell membranes and therefore are not associated with water shifts [36, 91]. Consequently, they do not cause hyponatraemia. In other words, although the presence of ineffective osmoles will make any existing hyponatraemia isomolar or hyperosmolar, the cause of hyponatraemia should be sought elsewhere. The serum is in fact hypotonic and water will still move from the extracellular to the intracellular compartment. It means patients are still at risk of brain oedema if hyponatraemia develops quickly. Examples of ineffective osmoles include urea, ethanol and methanol (**Table 7.10**).

Pseudohyponatraemia

Pseudohyponatraemia is a laboratory artefact that occurs when abnormally high concentrations of lipids or proteins in the blood interfere with the accurate measurement of sodium [30, 95, 96, 97]. Pseudohyponatraemia still occurs despite the use of ion-selective electrodes [30]. This is because venous blood samples are always diluted and a constant distribution between water and the solid phase of serum is assumed when the serum sodium concentration is calculated (**Figure 7.5**). This is called indirect ion-selective electrode measurement and used in large-scale analysers, e.g. in central laboratories. Serum osmolality is measured in an undiluted sample, and in case of pseudohyponatraemia (isotonic hyponatraemia), the result will be within the normal range. Other methods for diagnosing pseudohyponatraemia include direct potentiometry using a blood gas analyser (i.e. direct ion-specific electrode measurement) in which case no dilution of the sample occurs, or measurement of serum triglycerides, cholesterol and total protein concentration [30, 97, 98]. Differences between direct and indirect ion-specific electrode measurement of 5–10% have been reported in hypotonic hyponatraemia [99, 100]. Switching between indirect and direct ion-specific electrode measurements should be avoided in this situation.

- How did we translate this into a diagnostic strategy?

Because hyperglycaemia is by far the most common cause of non-hypotonic hyponatraemia, we have added excluding hyperglycaemic hyponatraemia in our diagnostic algorithm and detailed how it can be done. In addition, we have added excluding other causes of non-hypotonic hyponatraemia listed in **Table 7.10**. How this should be done is beyond the scope of this guideline.

The ability to measure serum osmolality may vary from centre to centre, especially out of office hours. During the discussions within the guideline development group, the importance of measured urine osmolality for the differential diagnosis of hyponatraemia was underscored. Hence, we reasoned it would be illogical not to recommend an additional

measurement of serum osmolality because it is not always available. However, although measuring serum osmolality in all patients with hyponatraemia may seem useful, there are no hard data confirming this improves diagnosis or outcome. Hence, we equally accept alternative approaches for ruling out non-hypotonic hyponatraemia. These approaches include evaluating the clinical context (e.g. infusion of mannitol or recent urological surgery), measuring the serum concentration of additional osmoles (e.g. urea, lactate and alcohol) or measuring the serum concentration of analytes that can cause pseudohyponatraemia (e.g. serum triglycerides, cholesterol and total protein).

Questions for future research

- Is the factor with which to correct the serum sodium concentration for glycaemia valid for all ranges of glycaemia and applicable to all patients?
- What is the incidence of pseudohyponatraemia?
- Does measuring serum osmolality in all patients with hyponatraemia improve the diagnostic process and outcomes of hyponatraemia?

Which parameters to be used for differentiating causes of hypotonic hyponatraemia?

- We recommend interpreting urine osmolality of a spot urine sample as a first step (1D).
- If urine osmolality is ≤ 100 mOsm/kg, we recommend accepting relative excess water intake as a cause of the hypotonic hyponatraemia (1D).
- If urine osmolality is > 100 mOsm/kg, we recommend interpreting the urine sodium concentration on a spot urine sample taken simultaneously with a blood sample (1D).
- If urine sodium concentration is ≤ 30 mmol/l, we suggest accepting low effective arterial volume as a cause of the hypotonic hyponatraemia (2D).
- If urine sodium concentration is > 30 mmol/l, we suggest assessing extracellular fluid status and use of diuretics to further differentiate likely causes of hyponatraemia (2D).
- We suggest against measuring vasopressin for confirming the diagnosis of SIADH (2D).

Advice for clinical practice

- Correct interpretation of laboratory measurements requires contemporaneous collection of blood and urine specimens.
- For practical reasons, urine osmolality and sodium concentration are best determined in the same urine sample.
- If clinical assessment indicates that the volume of extracellular fluid is not overtly increased and the urine sodium concentration is > 30 mmol/l, exclude other causes of hypotonic hyponatraemia before implicating SIAD. Consider using the diagnostic criteria listed in **Table 7.6** and look for known causes of SIAD.
- Consider primary or secondary adrenal insufficiency as an underlying cause of the hypotonic hyponatraemia.
- Kidney disease complicates differential diagnosis of hyponatraemia. Besides possibly

contributing to hyponatraemia, the ability of the kidneys to regulate urine osmolality and urine sodium is often diminished, much as with the use of diuretics. As urine osmolality and sodium may no longer reflect the effects of regular hormonal axes regulating sodium homeostasis, any diagnostic algorithm for hyponatraemia must be used with caution in patients with kidney disease.

- The water-loading test is generally not helpful for differential diagnosis of hypotonic hyponatraemia and may be dangerous in this setting.

Rationale

- Why this question?

Hypotonic hyponatraemia has many possible underlying causes. These include, but are not limited to, non-renal sodium loss, diuretics, third spacing, adrenal insufficiency, SIAD, polydipsia, heart failure, liver cirrhosis and nephrotic syndrome (see sections 5.6 and 5.8). Clinicians have traditionally used the clinical assessment of 'volume status' for classifying hyponatraemia as hypovolaemic, euvolaemic or hypervolaemic [87, 101, 102]. However, clinical assessment of volume status is generally not very accurate [90]. Hence, we wanted to know which tests are most useful in differentiating causes of hypotonic hyponatraemia, in which order we should use them and what threshold values have the highest diagnostic value.

- What did we find?

Clinical assessment of fluid status

We found two studies indicating that in patients with hyponatraemia, clinical assessment of volume status has both low sensitivity (0.5–0.8) and specificity (0.3–0.5) [89, 103]. Similarly, it seems that clinicians often misclassify hyponatraemia when using algorithms that start with a clinical assessment of volume status [88]. Using an algorithm in which urine osmolality and urine sodium concentration are prioritized over assessment of volume status, physicians in training had a better diagnostic performance than senior physicians who did not use the algorithm [104].

Urine osmolality

In the evaluation of hyponatraemia, urine osmolality is used to assess vasopressin activity [84]. Unfortunately, we found no study evaluating the sensitivity and specificity of a particular threshold. Physiologically, one would expect maximally dilute urine, in the presence of hypotonic hyponatraemia, unless hypo-osmolality fails to fully suppress vasopressin release. In hyponatraemia primarily caused by excess water intake, vasopressin release is suppressed resulting in urine osmolality usually <100 mOsm/kg [105]. By contrast, in case of non-suppressed vasopressin activity, urine osmolality usually exceeds serum osmolality [106]. This leaves a 'grey area' for urine osmolalities between 100 mOsm/kg and the value of the serum osmolality [84]. In this range, one cannot be clear about the presence or absence of vasopressin activity and excessive fluid intake may outweigh only moderately sup-

pressed vasopressin activity [85].

Urine sodium concentration

We found five studies assessing diagnostic accuracy of urine sodium concentration for differentiating hypovolaemia from euvolaemia or hypervolaemia. All studies used a rise in serum sodium concentration after the infusion of 0.9% sodium chloride as the reference standard for diagnosing hypovolaemia [89]. Four studies assessed the sensitivity and specificity of a urine sodium concentration >30 mmol/l for diagnosis of euvolaemia vs hypovolaemia [89, 103, 107, 108]. All found similarly high sensitivity estimates ranging from 0.87 to 1.0 but variable specificity estimates ranging from 0.52 to 0.83 [89, 103, 108]. Fenske et al. also included hypervolaemic patients. They assessed the same threshold for distinguishing hypovolaemia from euvolaemia and hypervolaemia but analysed patients with and without diuretics separately [107]. A urine sodium concentration >30 mmol/l had high estimated sensitivities of 1.0 and 0.94 respectively in patients off and on diuretics, but low specificities of 0.69 and 0.24 respectively [107]. Others evaluated the diagnostic accuracy of a urine sodium concentration >50 mmol/l [109] and >20 mmol/l [109] but found lower sensitivities and specificities respectively than with a threshold of 30 mmol/l.

Other laboratory tests

Several other diagnostic laboratory tests have been evaluated for their ability to distinguish euvolaemia from hypovolaemia and hypervolaemia in patients treated with and without diuretics. These tests include serum urea concentration, serum uric acid concentration, fractional sodium excretion, fractional uric acid excretion, fractional urea excretion and plasma copeptin concentration [103, 107, 108, 110]. Overall, fractional excretion of uric acid using a threshold of $>12\%$ seemed most useful for distinguishing hyponatraemia due to SIAD from non-SIAD hyponatraemia in patients under diuretics with a sensitivity of 0.86 and specificity of 1.0. In comparison with urine sodium concentration, fractional uric acid excretion may be a better test for differentiating hyponatraemia in patients who are also treated with diuretic therapy, but these results need to be confirmed in a separate cohort before this parameter can be recommended for routine use clinically [107].

Diagnostic difficulty with diuretics

The diagnostic difficulty we face with diuretics is that patients on these medications may have increased, normal or decreased extracellular and circulating volume and can have increased or decreased urine sodium concentration, depending on the timing of the most recent tablet, irrespective of their underlying volume status. The natriuresis induced by diuretics may cause 'appropriate' vasopressin release and subsequently hyponatraemia because of a decrease in circulating volume. Finally, diuretics may cause a SIAD-like state characterised by normal or mildly increased extracellular fluid volume [38, 111].

Urine sodium concentration can also be low in patients with heart failure or liver cirrhosis, due to reduced effective circulating arterial volume, even when they are taking diuretics (diuretic resistance) [112] (Appendix 6. Summary tables 1A and 1B).

- How did we translate the evidence into a differential diagnostic strategy?

We translated the diagnostic evidence into a diagnostic decision tree, leading to a point where specific underlying causes can be derived from the clinical setting or history (**Figure 7.6**). However, for obvious reasons, this diagnostic tree is a simplification and does not guarantee completeness in each individual. Of note, severely symptomatic hyponatraemia always requires immediate treatment, which should be prioritised over further diagnostic

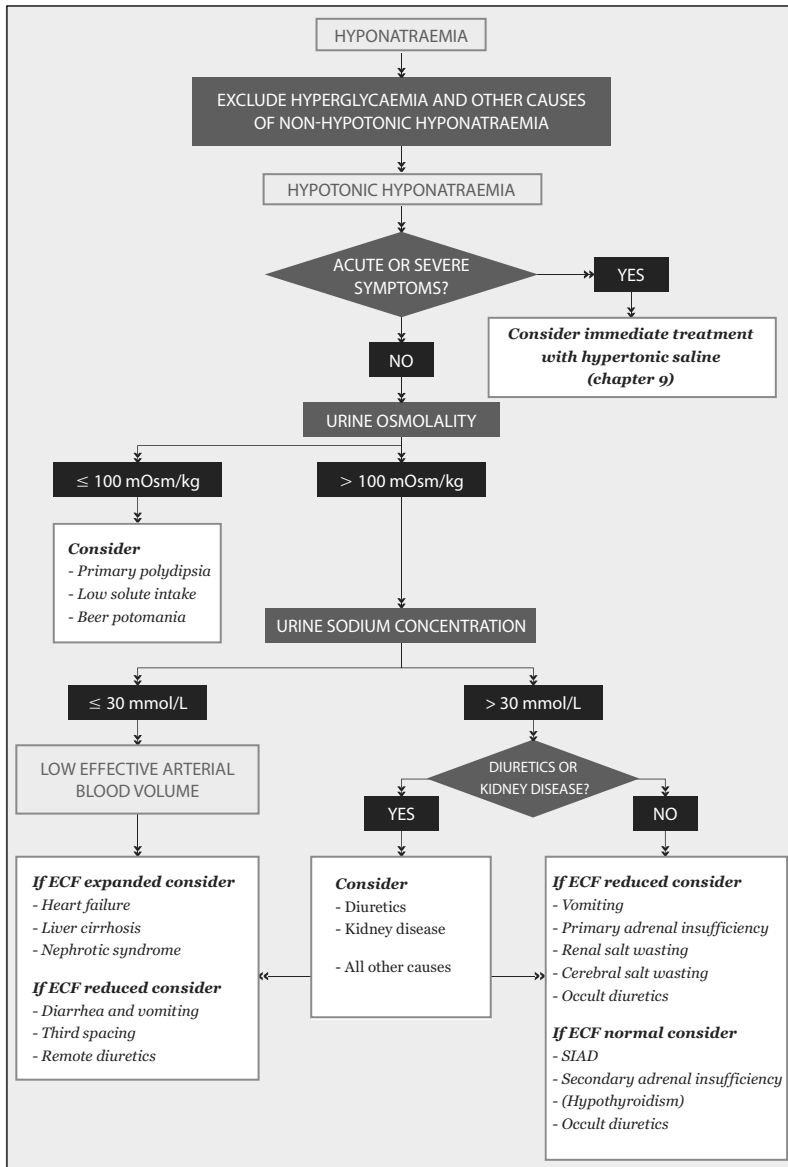


Figure 7.6. Algorithm for the diagnosis of hyponatraemia.

ECF – extracellular fluid

differentiation.

Urine osmolality

Although there are no diagnostic test accuracy studies assessing optimal thresholds for identifying vasopressin activity, a urine osmolality ≤ 100 mOsm/kg on a spot urine sample always indicates maximally dilute urine. Hyponatraemia primarily caused by excess water intake or (beer) potomania with low solute intake belongs to this category [53, 113]. Because determining urine osmolality is a simple method for confirming an excess of fluid intake relative to solute intake, we recommend it as a first step in the diagnostic strategy.

Urine sodium concentration

A urine osmolality > 100 mOsm/kg should trigger additional diagnostic testing to determine the underlying cause of hyponatraemia: ultimately classified into hyponatraemia with increased, normal or reduced extracellular fluid volume. Because clinical assessment of fluid status is often difficult and may lead clinicians down the wrong path, we have consciously steered away from the traditional approach of including it in the algorithm here. Instead, we recommend determining urine sodium concentration on a spot urine sample.

It is important to collect the serum and urine sample around the same time to allow correct interpretation of the values. We have selected a urine sodium concentration threshold of 30 mmol/l because several studies indicated good sensitivity and acceptable specificity in distinguishing hypovolaemia from euvoalaemia or hypervolaemia [89, 103, 107, 108]. This means that a urine sodium concentration ≤ 30 mmol/l suggests low effective arterial blood volume, even in patients on diuretics.

Diagnostic difficulty with diuretics

We suggest interpreting urine sodium concentrations > 30 mmol/l with caution if patients are taking diuretics. In patients using diuretics, a fractional excretion of uric acid $< 12\%$ may be better than urine sodium concentration to differentiate reduced effective circulating volume from SIAD as the underlying cause of hyponatraemia, although this assertion needs further confirmation [107]. We acknowledge that it may also be difficult to obtain the necessary measurements for calculating fractional uric acid excretion. For these reasons, we have refrained from advising to routinely calculate it in clinical practice.

Instead, we have taken a more pragmatic approach. First, we suggest that in patients taking diuretics, the diuretics be considered a contributing factor to hyponatraemia. Keep in mind that patients may not be aware they are taking diuretics or that their use may not have been recorded.

Although all types of diuretics have been associated with hyponatraemia, thiazide diuretics are most commonly the culprit [39]. Potassium-sparing diuretics such as mineralocorticoid receptor blockers and amiloride may also cause hyponatraemia. It occurs less frequently with loop diuretics because they interfere with the renal concentrating mechanism [17]. Importantly, the use of diuretics does not exclude other causes of hyponatraemia. Other causes require consideration especially if hyponatraemia persists after cessation of

the diuretic (unresolved hyponatraemia).

Clinical assessment of fluid status

In the absence of diuretics, a clinical assessment of the volume status may aid further differential diagnosis. Although we have avoided it previously, we feel using it this far down the algorithm is less likely to lead to misclassification. There are fewer possible causes and they are easier to distinguish from one another. Based on the combination of urine sodium concentration and clinical assessment of extracellular fluid volume, we can define four clinical categories that naturally suggest a number of underlying causes (**Figure 7.6**). The pathophysiology of these conditions is detailed in section 5.

Unresolved hyponatraemia

We have labelled hyponatraemia ‘unresolved’ if it persists after cause-specific treatment (see section 7). If hyponatraemia is unresolved, the initial diagnosis of the underlying cause was probably wrong or only part of the explanation. Reassessment using the diagnostic algorithm may help. One may also want to consider seeking expert diagnostic advice.

A special note on SIAD

SIAD is a diagnosis of exclusion. It fits the category of hyponatraemia with a urine osmolality >100 mOsm/kg, urine sodium concentration ≥ 30 mmol/l and normal extracellular fluid volume, but formal diagnosis requires exclusion of other possible causes of hyponatraemia. One such possible cause is adrenal insufficiency. In secondary adrenal insufficiency, hypocortisolism stimulates vasopressin release and like in SIAD, hyponatraemia develops through non-suppressed vasopressin activity [114, 115]. Primary adrenal insufficiency can present with hyperkalaemia and orthostatic hypotension but may occur without signs of reduced extracellular fluid volume and indeed resemble SIAD [40, 116, 117, 118]. Hyponatraemia due to hypothyroidism is very rare other than in myxoedema coma, when there is also a decrease in cardiac output and glomerular filtration rate [49, 51]. In 2006, Warner *et al.* [50] did identify a correlation between newly diagnosed hypothyroidism and decreased serum sodium but found this effect to be small and clinically irrelevant.

It is important to consider whether the diagnostic criteria for SIAD are met (**Table 7.6**) and look for known causes of inappropriate antidiuresis (Table 7. 7) [29, 45]. In theory, a diagnosis of SIAD requires all essential criteria to be met. If they are not, the presence of supplemental criteria increases the likelihood of SIAD. The original supplemental criteria for SIADH included an inappropriately elevated vasopressin concentration relative to serum osmolality. Although there was no systematic evaluation of the value of plasma vasopressin measurements, the guideline development group believed that it does not contribute to the diagnosis in practice, mainly due to the technical difficulties in measurement, and of interpretation due to the variable relationship between vasopressin concentrations and the resulting electrolyte-free water excretion. The guideline development group therefore feels that measurement of vasopressin cannot be recommended.

The original supplemental criteria for SIADH included an abnormal result of a water-load-

ing test to distinguish it from reset osmostat. However, we did not find data by which we could assess the value of water-loading tests. In addition, during group discussions, a fear of water-loading tests in patients with hypotonic hyponatraemia was expressed, as they may aggravate hypotonicity. Ultimately, it was decided to issue a warning against using it as a diagnostic test in SIAD.

Cerebral salt wasting is a rare condition that has been observed in patients with intracranial disorders such as subarachnoid bleeding [41]. It can reduce extracellular fluid volume due to profound natriuresis. A very high urine sodium concentration, a high serum urea, orthostatic hypotension and a low central venous pressure argue in favour of cerebral salt wasting (**Table 7.11**) [42].

Questions for future research

- What is the diagnostic performance of the new diagnostic algorithm included in this guideline?
- Can the addition of newer diagnostic parameters such as uric acid or copeptin or the replacement of the classical parameters by novel ones further improve the accuracy of the diagnosis of hyponatraemia?
- Is it still necessary to exclude hypothyroidism in the differential diagnosis of hyponatraemia?

Treatment of hypotonic hyponatraemia

How to use the treatment recommendations

The advice provided in this section follows a specific hierarchy as illustrated in **Figure 7.7**. Individual recommendations and statements can only be correctly interpreted and implemented if considered within this structure. This is a consequence of the choice to use different classifications for hyponatraemia, as explained in section 6.1.

Table 7.11. Differences between SIADH and cerebral salt wasting.

	SIADH	Cerebral salt wasting
Serum urea concentration	Normal – low	Normal – high
Serum uric acid concentration	Low	Low
Urine volume	Normal – low	High
Urine sodium concentration	> 30 mmol/L	>> 30 mmol/L
Blood pressure	Normal	Normal – orthostatic hypotension
Central venous pressure	Normal	Low

Adapted from Sherlock M et al. *Clin Endocrinol* 2006; 64: 250-254.

For a correct interpretation of the algorithm in question, it is crucial to understand that for correctly classifying symptoms as 'severe' or 'moderately severe', there must be sufficient confidence that the symptoms are caused by hyponatraemia. If hyponatraemia is mild and symptoms are severe or moderately severe (**Table 7.5**), the guideline development group advises to only accept causality in exceptional cases. Consequently, generally, sections 7.1, 7.2 and 7.3 are not applicable when hyponatraemia is mild.

It is also essential to understand that the guideline development group distinguishes between targets and limits. A target is a goal one is aiming for; it is the change in serum sodium concentration that one wishes and expects to achieve with a particular treatment.

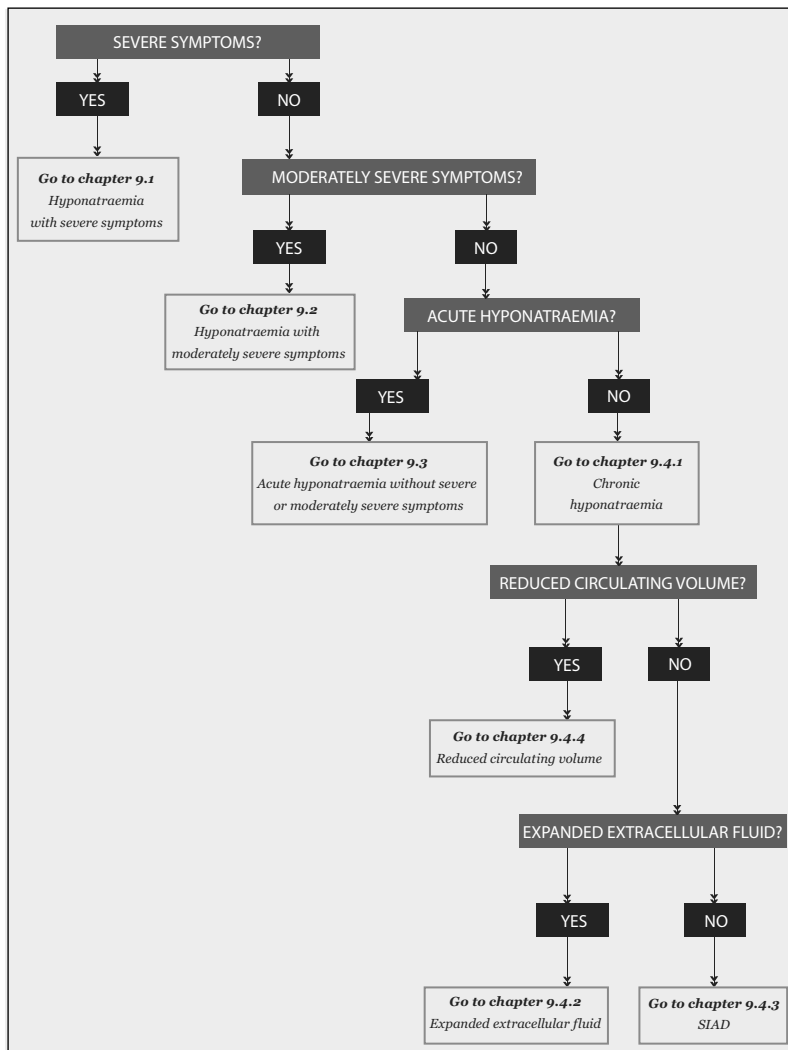


Figure 7.7. Algorithm for the management of hypotonic hyponatraemia.

By contrast, a limit is a change in serum sodium concentration one does not want to exceed and if surpassed, requires prompt counter-regulating intervention as described in section 7.5. In addition, the reader should bear in mind that the absolute numbers provided as 'targets' or 'limits' should always be interpreted in the clinical context of the individual patient.

Hyponatraemia with severe symptoms

First-hour management, regardless of whether hyponatraemia is acute or chronic

- We recommend prompt i.v. infusion of 150 ml 3% hypertonic over 20 min (1D).
- We suggest checking the serum sodium concentration after 20 min while repeating an infusion of 150 ml 3% hypertonic saline for the next 20 min (2D).
- We suggest repeating therapeutic recommendations 7.1.1.1 and 7.1.1.2 twice or until a target of 5 mmol/l increase in serum sodium concentration is achieved (2D).
- Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided (not graded).

Follow-up management in case of improvement of symptoms after a 5 mmol/l increase in serum sodium concentration in the first hour, regardless of whether hyponatraemia is acute or chronic

- We recommend stopping the infusion of hypertonic saline (1D).
- We recommend keeping the i.v. line open by infusing the smallest feasible volume of 0.9% saline until cause-specific treatment is started (1D).
- We recommend starting a diagnosis-specific treatment if available, aiming at least to stabilise sodium concentration (1D).
- We recommend limiting the increase in serum sodium concentration to a total of 10 mmol/l during the first 24 h and an additional 8 mmol/l during every 24 h thereafter until the serum sodium concentration reaches 130 mmol/l (1D).
- We suggest checking the serum sodium concentration after 6 and 12 h and daily afterwards until the serum sodium concentration has stabilised under stable treatment (2D).

Follow-up management in case of no improvement of symptoms after a 5 mmol/l increase in serum sodium concentration in the first hour, regardless of whether hyponatraemia is acute or chronic

- We recommend continuing an i.v. infusion of 3% hypertonic saline or equivalent aiming for an additional 1 mmol/l per h increase in serum sodium concentration (1D).
- We recommend stopping the infusion of 3% hypertonic saline or equivalent when the symptoms improve, the serum sodium concentration increases 10 mmol/l in total or the serum sodium concentration reaches 130 mmol/l, whichever occurs first (1D).
- We recommend additional diagnostic exploration for other causes of the symptoms than hyponatraemia (1D).
- We suggest checking the serum sodium concentration every 4 h as long as an i.v. infusion of 3% hypertonic saline or equivalent is continued (2D).

Advice for clinical practice

- Prompt infusion of hypertonic saline may save lives. However, preparing a 3% hypertonic saline infusion takes time and errors may occur in calculating the required amount of sodium chloride. Therefore, it may be wise for the pharmacy to store pre-prepared 150 ml bags of 3% hypertonic saline. It ensures that solutions are prepared under sterile conditions, by either the pharmacist or the manufacturer, and are available for immediate infusion without having to prepare them on the spot.
- Consider using weight-based (2 ml/kg) rather than the fixed 150 ml infusion volumes of 3% hypertonic saline in case of obviously deviant body composition.
- Do not expect patients with severe symptoms to completely recover immediately, as it may take some time for the brain to fully recover. Be aware that sometimes it may not be possible to assess an improvement in symptoms, e.g. because the patient is intubated and sedated. In these cases, we advise to follow guidance as described under 7.1.2.
- Keep in mind that if hypokalaemia is present, correction of the hypokalaemia will contribute to an increase in serum sodium concentration.
- To achieve the 1 mmol/l per h increase advised in 7.1.2.1, the formula of Adrogué–Madias may be used, but keep in mind that the actual increase may exceed the calculated increase [87]:

$$\text{Change in serum [Na}^+ \text{]} = \frac{\text{Infusate [Na}^+ \text{]} - \text{Serum [Na}^+ \text{]}}{\text{Total body water} + 1}$$

$$\text{Change in serum [Na}^+ \text{]} = \frac{(\text{Infusate [Na}^+ \text{]} + \text{Infusate [K}^+ \text{]}) - \text{Serum [Na}^+ \text{]}}{\text{Total body water} + 1}$$

Na⁺, sodium concentration (mmol/l); K⁺, potassium concentration (mmol/l). The numerator in formula 1 is a simplification of the expression in formula 2, with the value yielded by the equation (mmol/l). The estimated total body water (l) is calculated as a fraction of body weight. The fraction is 0.6 in non-elderly men and 0.5 in non-elderly women and 0.5 and 0.45 in elderly men and women respectively. Normally, extracellular and intracellular fluids account for 40 and 60% of total body water respectively.

Rationale

- Why this question?

When hyponatraemia causes severe symptoms, it reflects the presence of brain oedema. If not treated, death may rapidly follow. On the other hand, when hyponatraemia is chronic and the serum sodium concentration increases too rapidly, osmotic demyelination syndrome may develop and permanent brain damage may ensue. Infusion of hypertonic saline can rapidly raise the serum sodium concentration, but for clinicians, the indications, infusion speed and target serum sodium concentration are often unclear.

- What did we find?

Overall, the body of evidence to base recommendations for this topic was limited. Several early case series reported the use of i.v. hypertonic saline as treatment for hyponatraemia [119, 120, 121, 122, 123, 124,125]. However, settings, biochemical severity, rate of development, symptoms and co-interventions differed widely both between and within studies and were often difficult to assess. Insufficiently detailed reporting often made it difficult to assess the increases in serum sodium concentration that were attained and to what extent these studies were applicable to patients who present with severe symptoms according to our definitions.

In a case series published in 1982, seven patients with moderately severe to severe symptoms and profound hyponatraemia (mean serum sodium concentration 99 mmol/l) were treated with a 3% hypertonic saline i.v. infusion, resulting in a mean 2.4 ± 0.5 mmol/l per h increase in serum sodium concentration. Infusion rates differed between patients [120]. In 1986, Worthley et al. reported five patients who presented with seizures caused by acute hyponatraemia. They were treated with 250 mmol sodium chloride, infused over 10 min [119]. Serum sodium concentrations increased with a mean of 7.4 ± 1.1 mmol/l after 1 h and neurological symptoms promptly improved in all five cases. In a retrospective chart review of 11 patients with acute hyponatraemia, Hsu saw similar clinical outcomes. After infusion of 250–750 ml 3% NaCl, presenting symptoms of seizures and delirium resolved, although averaged initial increases in serum sodium concentration were limited to 1.6 ± 0.5 mmol/l per h [85].

Woo et al. retrospectively described the results of a fixed protocol for correcting acute hyponatraemia in 49 neurosurgical patients: a 3% hypertonic saline infusion, starting at 20 ml/h and adapted based on 6 h measurements of the serum sodium concentration. Serum sodium concentrations increased a mean 0.4 ± 0.4 mmol/l per h. There was minimal hyponatraemia [121]. The extent and type of symptoms were not reported.

We found one prospective non-comparative trial including 58 participants with profound hyponatraemia (mean serum sodium concentration 114 mmol/l) and moderately severe to severe symptoms. Patients were treated according to a protocol in which 100 ml 3% hypertonic saline was infused over 4 h with later adjustment according to biochemical response. After the initial infusion, the serum sodium concentration increased a median 2 mmol/l (range 0–6 mmol/l). In 22%, the serum sodium concentration did not increase after the first infusion and 19% required 200 ml while 3% required 300 ml for an initial increase of 1 mmol/l [126].

Mohmand *et al.* [122] retrospectively reported 62 cases of hyponatraemia treated with 3% hypertonic saline at a median infusion rate of 0.38 ml/kg per h. The treatment resulted in an average increase in serum sodium concentration of 0.5 ± 0.1 mmol/l per h with a mean total increase of 7.1 ± 0.6 mmol/l and 11.3 ± 0.7 mmol/l per h in the first and second 24 h. However, in 11 and 10% of cases, the increase was >12 mmol/l per 24 h and >18 mmol/l per 48 h respectively. Among patients with an initial serum sodium concentration <120 mmol/l, the observed increase in serum sodium concentration exceeded the rise predicted by the Adrogue–Madias formula in 74% of cases, on average 2.4 times the predicted rise. The ex-

tent of symptoms at presentation was not reported.

In another retrospective case series including 23 patients, Castello *et al.* [125] used another formula to calculate sodium deficit in hyponatraemic patients with liver cirrhosis. The sodium deficit was corrected with 3% hypertonic saline. There was a good correlation ($R = 0.98$) between the calculated sodium deficit and the amount of sodium used in correction. Symptoms resolved in all patients, but it is unclear to what extent symptoms were caused by hyponatraemia.

Forsell *et al.* reported a case series of six patients with chronic hyponatraemia due to heart failure treated with 3% hypertonic saline and i.v. loop diuretics. They observed an increase in serum sodium concentration and no deterioration of heart failure. However, no numeric data with the patient as unit of analysis and no symptomatology were provided [123].

Musch & Decaux observed 17 patients with chronic asymptomatic hyponatraemia due to SIAD treated with i.v. 0.9% saline. On average, the serum sodium concentration increased only slightly and indeed decreased in up to 1/3 of cases [124].

Sood *et al.* [127] assessed the efficacy of both 1–2 µg parenteral desmopressin and hypertonic saline for the correction of hyponatraemia in a single centre, retrospective cohort study including 24 patients. Hypertonic saline was infused at rates calculated to keep the increase in serum sodium concentration <6 mmol/l over 24 h (using the Adrogue–Madias formula). The combination treatment produced an increase in serum sodium concentration of 5.8 ± 2.8 mmol/l at 24 h and an additional 4.5 ± 2.2 mmol/l at 48 h. None of the patients had an increase in serum sodium concentration exceeding 12 mmol/l during the first 24 h or 18 mmol/l during the first 48 h. There was no significant difference between actual and predicted increases in serum sodium concentration during the first 24 h.

Osmotic demyelination syndrome is a rare but dramatic complication that occurs in chronic hyponatraemia when the serum sodium concentration increases too rapidly [128].

We found 54 cases (63% female, median age 45 years, interquartile range 45–58 years) of osmotic demyelination syndrome published since 1997: 45 individual case reports and three case series including a total of nine patients [72, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175]. In 96% (52/54), the diagnosis of osmotic demyelination syndrome was based on magnetic resonance imaging. Important details such as onset and cause of hyponatraemia, initial symptoms and their evolution, presence of other risk factors for osmotic demyelination syndrome and timing of osmotic demyelination syndrome symptoms in relationship to the increase in sodium concentration were generally poorly reported. In 6% (3/54), data were insufficient to allow estimation of the 24 and/or 48 h correction speed. In 96% (52/54) of cases, the initial serum sodium concentration was <120 mmol/l, in 85% (46/54) <115 mmol/l. In 87% (47/54), the sodium concentration increased ≥ 12 mmol/l during the first 24 h or ≥ 20 mmol/l during the first 48 h. Only 7% of cases (4/54) developed osmotic demyelination syndrome at lower correction rates [72, 136, 137, 165]. Two of these patients developed

osmotic demyelination syndrome with serum sodium concentration increases of 10– <12 mmol/l during the first 24 h and <18 mmol/l in 48 h [72,136]. Both patients (men) had a history of alcohol abuse as a risk factor for osmotic demyelination syndrome, and it is therefore unclear whether the neurological condition was caused by the speed of increase in serum sodium concentration. In another case, a woman with a history of alcohol abuse and hypokalaemia developed osmotic demyelination syndrome associated with an increase in serum sodium concentration limited to 2 mmol/l during 24 h and 4 mmol/l during 48 h [137]. Finally, in a further case, a woman developed osmotic demyelination syndrome after the serum sodium concentration increased by 15 mmol/l within the first 48 h of treatment; the 24 h limit could not be calculated. The quality of the reporting did not allow a reasonable assumption of causality [165] (Appendix 6. Summary tables 2A, 2B, 13A).

- How did we translate the evidence into the statement?

First-hour management

Severe symptoms mostly result from brain oedema caused by an acute drop in effective osmolality or by rapid further decrease in pre-existing chronic hyponatraemia [73]. Severely symptomatic hyponatraemia is a dangerous condition, which may lead to permanent brain damage or death if left untreated [73]. Although the available data stem from small series, they do suggest that the situation can be reversed by rapidly increasing the serum sodium concentration in the first hour [85, 119]. Given the immediate risk of severe neurological damage, reducing brain oedema should be prioritised in severely symptomatic hyponatraemia as this threat overrules that of possibly inducing osmotic demyelination or fluid overload.

If severe symptoms are caused by hyponatraemia, then small increases in effective osmolality by small increases in serum sodium concentration may be sufficient to improve them and to prevent brain stem herniation [119]. The infusion of 3% hypertonic saline is an effective way to rapidly increase the serum sodium concentration. Observational data and clinical experience indicate that a 5 mmol/l increase in serum sodium concentration can be sufficient to improve symptoms [176]. Most reports use a total of 500 ml of fluid. Although there is no evidence in published research to support the assertion, the guideline development group believed working with (repeated) 150 ml infusions, given every 20 min, may be a reasonable and safer approach. This approach allows monitoring of the change in serum sodium concentration in relationship to the clinical response and aims to manage the risk of overly rapid correction. We suggest repeating the 150 ml infusions of 3% hypertonic saline until the serum sodium concentration has increased 5 mmol/l, or until the symptoms improve, whichever comes first. There was no consensus in the guideline development group on whether these volumes are best given in continuous infusion (preferred by most) or by a slow i.v. injection. Some guideline development group members argued that the dose should be adapted to the weight of the patient, to avoid both over- and under-correction. Others argued that it may be difficult to assess weight correctly in the clinical environment

and that it was unclear whether actual weight or weight adjusted for body composition should be used (e.g. should obese patients have different weight-adjusted treatment regimens from muscular patients or patients with oedema). There was unanimous agreement that weight-dependent dose adaptation should be considered in patients with body composition clearly outside the range commonly seen in practice.

There was some concern regarding the availability of 3% hypertonic saline. The guideline development group agreed that hospitals should make an effort to have this solution available in their pharmacy. Prompt infusion of hypertonic saline may save lives and preparing a 3% hypertonic saline infusion takes time. In addition, errors may occur from having to calculate the required amount of sodium chloride in emergency.

Finally, given the severity of the neurological symptoms and the possibility of requiring airway protection or haemodynamic support, we feel these patients require management in an environment where close supervision can be provided.

Follow-up management: symptom improvement

If the symptoms improve after a 5 mmol/l increase in serum sodium concentration, we recommend stopping the infusion and starting cause-specific treatment to maintain the achieved serum sodium concentration. Systematic review of the cases of osmotic demyelination syndrome published during the past 15 years generally supports restricting increases in serum sodium concentration <10 mmol/l in the first 24 h and <18 mmol/l in the first 48 h. It is very difficult, if not impossible, to set 'safe' rate limits for correcting hyponatraemia. The risk of developing the osmotic demyelination syndrome seems to depend not only on the rate of increase in serum sodium concentration but also on associated underlying risk factors, such as a history of alcohol abuse, liver disease, use of thiazides or antidepressant medications and the original biochemical degree and duration of hyponatraemia. Although case-based data do not allow incidence or risk estimation, only two cases of osmotic demyelination syndrome have been reported with correction speeds below these limits.

We should reemphasise that limits are different from aims. The capacity of the kidneys to excrete electrolyte-free water can vary substantially during treatment and the actual change in serum sodium concentration may be unpredictable. Correction speeds frequently exceed those predicted by the Adrog  -Madias formula, even by as much as five times that predicted [122]. This reflects interplay between a number of factors: suppression of appropriate endogenous vasopressin secretion by fluid and salt loading, the natural history of the underlying condition and the potential impact of cause-specific treatments. Given the uncertainty in biochemical response to treatment, the guideline development group believes that the increase in serum sodium concentration aimed for initially should be sufficient to allow an appropriate margin of safety. Based on an extensive systematic review of available case reports, the guideline development group agreed that a correction rate of 10 mmol/l during the first 24 h and 18 mmol/l during the first 48 h is probably a safe limit.

We advise close monitoring of serum sodium concentrations during the first 24 h of treatment and daily thereafter. It can be speculated that administering desmopressin makes the

Androgué–Madias formula more accurate in clinical practice, as it removes one of the variables during treatment, by clamping urine electrolyte-free water excretion at a constant level. A retrospective observational study has indicated that combined use of 1–2 µg i.v. desmopressin with hypertonic saline may allow gradual increase in serum sodium concentration without risking overcorrection. The study involved physicians with extensive experience in treating hyponatraemia. The guideline development group believes that these results are interesting but require confirmation before advocating it as a general practice. For management in case of accidental overcorrection, we refer to section 7.5.

Follow-up management: no symptom improvement

If the symptoms do not improve after a 5 mmol/l increase in serum sodium concentration during the first hour, other explanations for the symptoms should be explored. Depending on the clinical history, additional neurological investigations such as imaging may be helpful. We advise attempting a further increase in serum sodium concentration of 1 mmol/l by infusing 3% hypertonic saline while additional avenues are explored. If symptoms do not improve after a 10 mmol/l increase in serum sodium concentration, it is (even more) likely they are caused by something other than hyponatraemia. Hence, we believe that serum sodium concentration should not increase >10 mmol/l during the first 24 h (the first 5 mmol included), even if symptoms do not improve. The guideline development group also recommends stopping hypertonic saline if the serum sodium concentration reaches 130 mmol/l. Similar to the reasoning above, it is unlikely that symptoms are caused by hyponatraemia if they persist after the serum sodium concentration has reached 130 mmol/l.

Suggestions for future research

- Development and testing of assessment models (based on easily measurable variables such as height, sex and weight) that would enable accurate and reliable prediction of the expected increase in serum sodium concentration in response to a given i.v. sodium load.
- Prospective, standardised, multicentre registry to collect data relating to the increase in serum sodium concentration and clinical response and to facilitate determining the safe upper speed limit for correcting hyponatraemia.

Hyponatraemia with moderately severe symptoms

- We recommend starting prompt diagnostic assessment (1D).
- Stop, if possible, medications and other factors that can contribute to or provoke hyponatraemia (not graded).
- We recommend cause-specific treatment (1D).
- We suggest immediate treatment with a single i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).
- We suggest aiming for a 5 mmol/l per 24-h increase in serum sodium concentration (2D).
- We suggest limiting the increase in serum sodium concentration to 10 mmol/l in the first 24 h and 8 mmol/l during every 24 h thereafter, until a serum sodium concentration of

130 mmol/l is reached (2D).

- We suggest checking the serum sodium concentration after 1, 6 and 12 h (2D).
- We suggest additional diagnostic exploration for other causes of the symptoms if the symptoms do not improve with an increase in serum sodium concentration (2D).
- We suggest considering to manage the patient as in severely symptomatic hyponatraemia if the serum sodium concentration further decreases despite treating the underlying diagnosis (2D).

Rationale

- Why this question?

Hyponatraemia with moderately severe symptoms is a dangerous condition. Although the immediate threat to life is less pronounced than for hyponatraemia with severe symptoms, any further decline in serum sodium concentration can cause the clinical situation to deteriorate very rapidly. However, were the serum sodium concentration to increase too rapidly, osmotic demyelination syndrome might develop if hyponatraemia is chronic and permanent brain damage may ensue. For clinicians, it is often unclear which treatments should be used or what increases in serum sodium concentration they should pursue.

- What did we find?

Overall, the body of evidence on which to base recommendations was very limited and similar to that for hyponatraemia with severe symptoms (see section 7.1).

- How did we translate the evidence into the statement?

Although hyponatraemia with moderately severe symptoms is a dangerous condition, the immediate threat is less pronounced than for hyponatraemia with severe symptoms. Consequently, in the balance between benefits and harms, the reduced immediate threat from hyponatraemia shifts the priority to preventing a further decrease in serum sodium concentration rather than inducing a rapid increase. The target increase in serum sodium concentration we advise, therefore, is also smaller and the motivation for infusing hypertonic saline is less strong. In our opinion, there is time for diagnostic testing and treatment can be directed towards the specific diagnosis.

Suggestions for future research

None.

Acute hyponatraemia without severe or moderately severe symptoms

- Make sure that the serum sodium concentration has been measured using the same technique used for the previous measurement and that no administrative errors in sample handling have occurred (not graded).
- If possible, stop fluids, medications and other factors that can contribute to or provoke

hyponatraemia (not graded).

- We recommend starting prompt diagnostic assessment (1D).
- We recommend cause-specific treatment (1D).
- If the acute decrease in serum sodium concentration exceeds 10 mmol/l, we suggest a single i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).
- We suggest checking the serum sodium concentration after 4 h, using the same technique as used for the previous measurement (2D).

Rationale

- Why this question?

We have defined 'acute' hyponatraemia as hyponatraemia that is documented to exist <48 h (section 6.1.2). Although the absence of moderately severe to severe symptoms indicates that the patient is not suffering clinically important brain oedema, adaptation has not occurred and any further decline in serum sodium concentration may rapidly worsen the clinical situation. Because adaptation has not been completed, the theoretical risk of osmotic demyelinating syndrome through overly rapid correction is less of a worry. For clinicians, it is often unclear which treatments should be used or what increases in serum sodium concentration they should pursue.

- What did we find?

We found one pseudo-randomised trial including eight participants of the 161 km long 2009 Western States Endurance Run, who had a serum sodium concentration <135 mmol/l at the end of their run without neurological symptoms. Participants were randomised based on their registration number to either oral rehydration with 100 ml 3% hypertonic saline solution or a single i.v. infusion of 100 ml 3% saline. After 1 h, the serum sodium concentration was 4.3 mmol/l higher for the participants receiving i.v. fluids than for the patients receiving oral rehydration. Reliability of the results was affected by a 1 mmol/l higher serum sodium concentration at baseline in patients receiving i.v. fluids, inadequate randomisation, lack of untreated controls and the open-label design (Appendix 6. Summary tables 2A and 2B).

- How did we translate the evidence into the statement?

As is often the case for hyponatraemia, the evidence for a particular management strategy in patients with acute hyponatraemia without moderately severe or severe symptoms is poor. Hence, recommendations are largely based on translation from physiology, laboratory and animal data and clinical experience. The absence of severe symptoms indicates that the brain has not yet developed clinically important brain oedema. Similarly to hyponatraemia with moderately severe symptoms, it shifts the priority from inducing a rapid increase to preventing a further decrease in serum sodium concentration. Again, the motivation for infusing hypertonic saline is less strong than for hyponatraemia with severe symptoms. In the opinion of the guideline development group, there is time for diagnostic testing. Treatment can be diagnosis specific, although a single infusion of 150 ml 3% hypertonic saline may be

wise to avoid a further drop in serum sodium concentration regardless of underlying cause.

Because the brain has not had the time to adapt fully to its hypotonic environment when hyponatraemia is acute, we believe the risk of osmotic demyelination after overly rapid increase is less of a concern. The available data on osmotic demyelinating syndrome seem to support that this position is correct. This is why we set no limit or aim for the correction in acute hyponatraemia. This contrasts with our recommendations for hyponatraemia with moderately severe or severe symptoms because in these settings we advise to initiate treatment regardless of whether hyponatraemia is acute or chronic.

Different techniques to measure serum sodium concentration might result in different results. Therefore, when a sudden decrease in serum sodium concentration between two measurements is observed, it is advisable to first check consistency of measurement.

Suggestions for future research

Prospective, large-scale, registration-based data collection to facilitate impact evaluation of the proposed management strategy on end-points of clinical response and overcorrection rate.

Chronic hyponatraemia without severe or moderately severe symptoms

General management

- Stop non-essential fluids, medications and other factors that can contribute to or provoke hyponatraemia (not graded).
- We recommend cause-specific treatment (1D).
- In mild hyponatraemia, we suggest against treatment with the sole aim of increasing the serum sodium concentration (2C).
- In moderate or profound hyponatraemia, we recommend avoiding an increase in serum sodium concentration of >10 mmol/l during the first 24 h and >8 mmol/l during every 24 h thereafter (1D).
- In moderate or profound hyponatraemia, we suggest checking the serum sodium concentration every 6 h until the serum sodium concentration has stabilised under stable treatment (2D).
- In case of unresolved hyponatraemia, reconsider the diagnostic algorithm and ask for expert advice (not graded).

Patients with expanded extracellular fluid

- We recommend against a treatment with the sole aim of increasing the serum sodium concentration in mild or moderate hyponatraemia (1C).
- We suggest fluid restriction to prevent further fluid overload (2D).
- We recommend against vasopressin receptor antagonists (1C).
- We recommend against demeclocycline (1D).

Patients with SIAD

- In moderate or profound hyponatraemia, we suggest restricting fluid intake as first-line treatment (2D).
- In moderate or profound hyponatraemia, we suggest the following can be considered equal second-line treatments: increasing solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral sodium chloride (2D).
- In moderate or profound hyponatraemia, we recommend against lithium or demeclocycline (1D).
- In moderate hyponatraemia, we do not recommend vasopressin receptor antagonists (1C).
- In profound hyponatraemia, we recommend against vasopressin receptor antagonists (1C).

Patients with reduced circulating volume

- We recommend restoring extracellular volume with i.v. infusion of 0.9% saline or a balanced crystalloid solution at 0.5–1.0 ml/kg per h (1B).
- Manage patients with haemodynamic instability in an environment where close biochemical and clinical monitoring can be provided (not graded).
- In case of haemodynamic instability, the need for rapid fluid resuscitation overrides the risk of an overly rapid increase in serum sodium concentration (not graded).

Advice for clinical practice

- A sudden increase in urine output to >100 ml/h signals increased risk of overly rapid rise in serum sodium concentration. If vasopressin activity is suddenly suppressed, as happens when intravascular volume is restored in hypovolaemia, free water clearance can dramatically increase, resulting in serum sodium concentrations rising more rapidly than expected. If urine output suddenly increases, we would advise measuring the serum sodium concentration every 2 h until it has stabilised under stable treatment. The implicit advice to monitor urine output does not imply that we advise a bladder catheter solely for this purpose. Most patients will be able to void spontaneously and collect urine for output monitoring.
- As a means of increasing solute intake, we suggest daily intake of 0.25–0.50 g/kg urea can be used. The bitter taste can be reduced by combining it with sweet-tasting substances. The pharmacist may be asked to prepare the following as sachets: urea 10 g + NaHCO₃ 2 g + citric acid 1.5 g + sucrose 200 mg to be dissolved in 50–100 ml water. This will result in a more palatable, slightly sparkling solution.

Rationale

- Why this question?
Chronic hyponatraemia is common and associated with an increased risk of death, both

in and out of hospital [17]. However, it is unclear whether risk of death further increases as individual sodium concentrations decrease, and data on the exact association between serum sodium concentration and death are contradictory [19]. In addition, it remains unclear whether hyponatraemia itself or the underlying disease explains the higher mortality risk. It is also unclear whether treating hyponatraemia improves patient outcome. Finally, even if we decide to treat, it is often unclear what treatment option is most appropriate.

- What did we find?

We identified two systematic reviews comparing a vasopressin receptor antagonist (one of conivaptan, lixivaptan, satavaptan or tolvaptan) vs placebo. A first review, published in 2010, included 15 randomised controlled trials and 1619 participants up to 2009 [177]. Overall, vasopressin receptor antagonists modestly increased serum sodium concentration after 3–7 days (mean difference (MD) 5.27 mmol/l, 95% CI 4.27–6.26) and up to 1 month (MD 3.49 mmol/l, 95% CI 2.56–4.41). There was no significant reduction in risk of death and there were similar numbers of adverse and serious adverse events. Although there had been no reports of osmotic demyelination syndrome, risk of a rapid increase in serum sodium concentration was 10% when treated with a vasopressin receptor antagonist and 2.5 times higher than when treated with placebo (relative risk (RR) 2.52, 95% CI 1.26–5.06).

A second review, published in 2011, included 11 randomised trials and 1094 participants up to May 2010 [178]. Overall, results were consistent with the earlier review. There was a modest increase in serum sodium concentration at 5 days (MD 5.70, 95% CI 4.10–7.40) and up to 1 month (MD 4.60, 95% CI 3.60–5.50). There was no significant reduction in risk of death (odds ratio (OR) 0.67, 95% CI 0.38–1.18), no significant increased risk of adverse events, no reports of osmotic demyelination syndrome but a three times higher odds for rapid increases in serum sodium concentration (OR 3.03, 95% CI 1.82–5.05).

We identified five additional trials published since 2010, increasing the total sample size to 20 trials and 2900 participants [179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197]. Overall, most participants had only mild to moderate hyponatraemia at onset with average sodium concentrations ranging between 124 and 135 mmol/l. Quality of the evidence was generally reduced by risk of bias due to difficulties with blinding participants, potentially unbalanced use of fluid restriction, incomplete outcome reporting and industry sponsorship. When we updated the earlier meta-analyses by Rozen-Zvi *et al.* with the additional data, we found that compared with placebo, vasopressin receptor antagonists did not reduce the number of deaths (RR 1.08, 95% CI 0.80–1.46). When study results were sub-grouped according to volume status, a signal appeared indicating a possibly increased risk of death for hypervolaemic patients treated with a vasopressin receptor antagonist in comparison with placebo. However, results were not statistically significant and sample sizes were small (Appendix 6, Summary tables 10A and 10B). No study reported a measure of quality of life, validated for hyponatraemia [188]. Combined analysis showed a modest increase in serum sodium concentration in the vasopressin antagonist group vs placebo both at 3–7 days (MD 4.30, 95% CI 3.51–4.95 mmol/l)

and up to 7 months (MD 3.49 mmol/l, 95% CI 3.59–5.02). There was no difference in adverse events (RR 1.01, 95% CI 0.94–1.09), serious adverse events (RR 1.04, 95% CI 0.91–1.20) or adverse events requiring drug discontinuation (RR 0.85, 95% CI 0.61–1.19) in patients with hyponatraemia. However, the risk for rapid sodium increase was 60% higher when treated with a vasopressin receptor antagonist (RR 1.61, 95% CI 1.11–2.33), indicating that per 1000 patients treated, 26 more would have an overly rapid correction. Results were consistent across different vasopressin receptor antagonists (tolvaptan, conivaptan, lixivaptan and satavaptan) and thresholds for rapid sodium correction, indicating a class effect. We found no published reports of osmotic demyelination syndrome occurring after an overly rapid increase during treatment with a vasopressin receptor antagonist. In March 2012, however, the company marketing tolvaptan issued a statement saying that there had been reports of neurological sequelae in patients treated with tolvaptan where the correction of serum sodium had exceeded the suggested rate [198]. In April 2013, the U.S. Food and Drug Administration issued a Drug Safety communication based on serious adverse events in a trial where tolvaptan was studied as treatment for delaying the evolution of autosomal dominant polycystic kidney disease [199]. Three patients developed serious liver injury, the earliest case 3 months after initiating tolvaptan. In addition, 42 of 958 participants (4.4%) treated with tolvaptan vs five of 484 (1.0%) treated with placebo developed alanine aminotransferase elevations greater than three times the upper limit of normal [200]. Drug doses administered were higher than those that were used in hyponatraemia.

We found one trial (nine participants) that compared oral demeclocycline vs placebo, reporting only a modest and non-significant difference in serum sodium concentration increase at 3 weeks (MD 2.7 mmol/l, 95% CI –0.7 to 6.2) [201]. We identified no systematic reviews or randomised controlled trials evaluating the benefits and harms of urea, lithium, mannitol, loop diuretics, phenytoin or fluid restriction. We found several case series demonstrating an increase in serum sodium concentration after 2–7 days for urea [202, 203, 204, 205, 206], demeclocycline [207], loop diuretics in combination with oral NaCl [123, 125, 208], phenytoin [209] and fluid restriction [210]. We also identified case series of patients experiencing an increase in serum sodium over a longer time period of up to 12 months for urea [211, 212, 213], up to 3 weeks for demeclocycline [214, 215, 216, 217, 218, 219], up to 20 weeks for lithium [220], up to 150 days for furosemide with oral NaCl [221] and up to 30 days in phenytoin [220].

We also found several observational reports of acute kidney injury with demeclocycline [214, 215, 218, 219, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232]; a single case report of confusion and somnolence with lithium [220] and unspecified neurological abnormalities with phenytoin [233]. Finally, we identified two reports of adverse events with fluid restriction. The first was a retrospective study using data generated in a randomised controlled trial evaluating tranexamic acid in patients with severe subarachnoid bleeding. In 44 participants with hyponatraemia, 80% developed subsequent cerebral infarction when given <1000 ml of fluids a day vs 33% when not fluid restricted. The very specific setting makes the data of limited value to other settings. The small sample size, lack of adjustment

for confounding and the heterogeneity of hyponatraemia within the study group limit its value for causal inference. The second study included two cases of osmotic demyelination syndrome that occurred after restriction of fluid intake to 750 ml daily. The first case occurred in a man with hyponatraemia probably due to polydipsia and low solute intake, the second in a woman with hyponatraemia due to thiazides, which were stopped on admission. In both cases, the serum sodium concentration increased with >19 mmol/l during the first 24 h and causal association between fluid restriction and subsequent demyelination appear to be limited [234, 235] (Appendix 6. Summary tables 3A to 12B).

- How did we translate the evidence into the statement?

General management

Many people take medications that can provoke or contribute to hyponatraemia. It makes sense to check whether patients with hyponatraemia are taking any such medications, to reconsider their necessity and to stop them if perceived benefits do not outweigh perceived harms. Likewise, it seems logical to stop unnecessary fluids, discourage excessive oral water drinking and treat any underlying condition that can be improved.

We found no comparative studies of the different available treatment strategies for chronic hyponatraemia. Taking into account the absence of evidence that treating chronic hyponatraemia results in improvement of patient-relevant outcomes, the guideline development group judged that our primary concern was avoiding harm through treatment.

In patients with chronic mild hyponatraemia, we found no evidence that correcting hyponatraemia itself improves patient-important outcomes. All interventions can cause adverse events. We therefore advise against active interventions with the sole aim of increasing the serum sodium concentration.

One could argue the same holds for moderate or even profound hyponatraemia. For these conditions too, there is little or no evidence to support treatment. However, different members in the guideline development group felt uncomfortable in advocating no treatment for moderate or profound chronic hyponatraemia, highlighting the risk of a sudden, further deterioration leading to severe or moderately severe symptoms. Therefore, it was accepted that the risk–benefit balance for the different biochemical degrees of chronic hyponatraemia, and of the underlying diagnosis, would be evaluated separately.

One important, potential harm is development of osmotic demyelination syndrome when the serum sodium concentration rises too rapidly. Systematic review of the cases of osmotic demyelinating syndrome published during the past 15 years generally support avoiding increases in serum sodium concentration >10 mmol/l in the first 24 h and >18 mmol/l in the first 48 h, regardless of treatment type. It is very difficult, if not impossible, to set ‘safe’ speed limits for rate of correction. Risk of development of osmotic demyelination syndrome seems to depend not only on the speed of increase in serum sodium concentration but also on associated underlying risk factors: alcohol abuse, liver disease, use of thiazides or antidepressant medications, the original biochemical degree and the duration of

hyponatraemia. Although case-based data do not allow incidence or risk estimation, only two cases have been reported with correction speeds below these limits. In the majority of cases, correction speeds largely exceed them. We should be clear that limits are different from aims. As there is no clear evidence that correcting chronic hyponatraemia improves patient-important outcomes, we did not formulate aims. If you wish to avoid surpassing a certain 24-h limit, serum sodium concentration needs to be measured more frequently than once daily to allow adjusting treatment to the observed change. The 6-h measurement is somewhat arbitrary, chosen to manage a balance between allowing change in treatment and practicality. At this point in time, there are insufficient data on incidence of osmotic demyelination syndrome and influence of measurement timing to give a more informed view.

Expanded extracellular fluid volume

There are insufficient data to suggest that increasing serum sodium concentration improves patient-important outcomes in moderate hyponatraemia with expanded extracellular fluid volume, such as seen in liver cirrhosis or heart failure. Given treatments directed solely at increasing serum sodium concentration have inherent risks of overcorrection and other adverse effects, we believed that the balance was in favour of not treating in case of mild or moderate hyponatraemia in patients with expanded extracellular volume. For patients with profound hyponatraemia in this setting, the guideline development group acknowledged that it might be reasonable to avoid further decreases in serum sodium in certain patients, although there are no published data to support this view. Hence, the guideline development group refrained from making any statement regarding whether or not to treat this category of patients. Clearly, fluid restriction in this setting can be used as a means to reduce further fluid overload.

On systematic review of data in this specific patient category, there appeared to be an increased number of deaths in those patients treated with vasopressin receptor antagonists in comparison with those treated with placebo. Although results were not statistically significant and sample sizes were small, the guideline development group believed the signal that active treatment may actually worsen outcomes was sufficient to recommend against vasopressin receptor antagonists in this specific category. The side effects reported for demeclocycline and lithium were such that we recommend not using them for any degree of hyponatraemia.

Syndrome of inappropriate antidiuresis

Although there is little to no formal evidence that fluid restriction increases serum sodium concentration more than placebo, clinical experience generally supports its use, provided fluid restriction is strictly adhered to. Similarly, there is no good evidence that fluid restriction is associated with important adverse effects, other than poor patient acceptability. In the cases mentioned above, we believed it was unlikely that fluid restriction played a causal role in the development of osmotic demyelination syndrome. Hence, the guideline development group unanimously preferred fluid restriction as first-line treatment. As a second-line treatment, we suggest an increased intake of osmotic solutes to enhance clear-

ance of water. We agreed that oral urea might be the most practical method to achieve increased solute intake. The guideline group acknowledged the bitter taste of urea, which might reduce acceptability. However, we believed that this could be solved by combining urea with sweet-tasting substances as described in the recipe provided in the advice for clinical practice. The guideline development group did not consider availability of urea a problem as it is used in many other pharmacological preparations.

For demeclocycline and lithium, there is some evidence of possible harm, so we advise against their use for management of any degree of chronic hyponatraemia in patients with SIAD.

Although vasopressin receptor antagonists do increase serum sodium, the guideline development group judged that based on current evidence, these drugs cannot be recommended. Indeed, the risk benefit ratio seems to be negative: there is no proven outcome benefit aside from increase in serum sodium concentrations, while there are increasing concerns on safety. The most prominent safety-related factor is the increased risk for overly rapid correction of hyponatraemia. As this risk is greatest in patients with profound hyponatraemia, the guideline development group wanted to recommend against the use of vasopressin receptor antagonists in this specific patient group. In addition, our concern around the toxicity profile of these compounds was increased by reports from the U.S. Food and Drug Administration warning for hepatotoxicity associated with the use of high tolvaptan doses in autosomal dominant polycystic kidney disease.

Patients with contracted extracellular volume

Hyponatraemia with reduced extracellular fluid volume may require a different approach to other causes of hyponatraemia. Patients with hyponatraemia and a contracted extracellular fluid volume have a combination of a true sodium and water deficit. They also have appropriate vasopressin secretion and hence diminished electrolyte-free water clearance, simultaneously resulting in dilutional hyponatraemia. Although hyponatraemia with reduced extracellular fluid volume is common in clinical practice, we did not find specific studies addressing management from the perspective of treating hyponatraemia. Given the absence of formal evidence in this setting, recommendations are based on direct translation of pathophysiology to clinical practice.

Patients with hyponatraemia and reduced extracellular fluid volume lack water as well as sodium. Consequently, replenishing both deficits with isotonic saline seems logical. However, isotonic saline is characterised by an unphysiologically high concentration of chloride, which may impair renal function. Recent data have indicated that balanced crystalloid solutions might be preferable for restoring volume deficits and these solutions are now commonly recommended in guidelines on volume replacement, although there is no published research specifically for hyponatraemia available [236, 237, 238].

If hyponatraemia is caused by a contracted extracellular fluid volume, restoring this volume will suppress vasopressin secretion causing electrolyte-free water excretion to increase. Therefore, these patients are at high risk of an overly rapid increase in serum sodium

concentration. Sudden increases in urine output can act as a warning signal that overly rapid correction of hyponatraemia is imminent.

In patients who are haemodynamically unstable, the immediate risk of decreased organ perfusion is more important than the potential risk of overly rapid increases in serum sodium concentration. Hence, the need for volume resuscitation overrides any concerns for overly rapid correction of hyponatraemia. These patients are best managed in an environment where close monitoring, including frequent and swift sampling of serum and determination of its sodium concentration, is possible. In the case of imminent overcorrection, we suggest to continue fluid loading (if still needed) with free water, e.g. glucose solutions.

Suggestions for future research

More high-quality randomised, head-to-head comparison trial data for all potential treatments using longer term health outcomes such as death, quality of life and cognitive function.

What to do if hyponatraemia is corrected too rapidly?

- We recommend prompt intervention for re-lowering the serum sodium concentration if it increases >10 mmol/l during the first 24 h or >8 mmol/l in any 24 h thereafter (1D).
- We recommend discontinuing the ongoing active treatment (1D).
- We recommend consulting an expert to discuss if it is appropriate to start an infusion of 10 ml/kg body weight of electrolyte-free water (e.g. glucose solutions) over 1 h under strict monitoring of urine output and fluid balance (1D).
- We recommend consulting an expert to discuss if it is appropriate to add i.v. desmopressin 2 µg, with the understanding that this should not be repeated more frequently than every 8 h (1D).

Rationale

- Why this question?

Interrupting the underlying mechanisms that cause hyponatraemia can lead to sudden and rapid increases in serum sodium concentration. Overly rapid increases in serum sodium concentration can have dramatic consequences if osmotic demyelinating syndrome develops. For clinicians, it is often unclear what to do when overly rapid correction occurs.

- What did we find?

Although the exact incidence of overly rapid correction is unknown and depends on its definition, overly rapid increases in serum sodium concentration appear to be common. A small retrospective single-centre study including 62 participants treated with hypertonic saline reported correction in 11% at 24 h and in an additional 10% at 48 h [122].

Among those with a serum sodium concentration <120 mmol/l, the observed increase exceeded the rise predicted by the Adrogue–Madias formula in 74%. In patients with overly

rapid correction, the average increase in serum sodium concentration was 2.4 times that of the predicted increase. Inadvertent overly rapid correction was due to documented water diuresis in 40% of cases.

We found no randomised controlled trials and only two small observational studies on interventions for reversing overly rapid correction of hyponatraemia. In the first of these, a retrospective single-arm cohort study, six patients were given desmopressin after a 24-h increase in serum sodium concentration of 12 mmol/l had already been reached. Correction exceeding a 48-h limit of 18 mmol/l was avoided in five of the six. An additional 14 patients were given desmopressin in an attempt to prevent overcorrection after serum sodium concentration had increased 1–12 mmol/l. All patients had corrections below the 24- and 48-h limits [239].

The second, a small single-centre single-arm retrospective cohort study included 24 participants [127]. A combination of 1–2 µg parenteral desmopressin and hypertonic saline was infused at speeds calculated (using the Adrogue–Madias formula) to keep the increase in serum sodium concentration <6 mmol/l over 24 h. The combined treatment produced an increase in serum sodium concentration of 5.8 ± 2.8 mmol/l at 24 h and an additional 4.5 ± 2.2 mmol/l at 48 h. None of the patients had an increase in serum sodium concentration exceeding 12 mmol/l during the first 24 h or 18 mmol/l during the first 48 h. There was no significant difference between actual and predicted increases in serum sodium concentration during the first 24 h.

- How did we translate the evidence into the statement?

The incidence of overly rapid correction of hyponatraemia depends on the thresholds used to define overly rapid correction. The limited data we have seem to indicate that serum sodium concentrations are increased >10 mmol/l during the first 24 h and >8 mmol/l every 24 h thereafter fairly frequently. The incidence of osmotic demyelinating syndrome resulting from overly rapid increases in serum sodium concentration is unknown. As information in this area is still only derived from case reports and small case series, it is probably very low. Given the dramatic consequences of osmotic demyelinating syndrome, it is clear that overly rapid increases should be avoided when treatment for hyponatraemia is started. Similarly, it makes sense to stop the active treatment of hyponatraemia if the increase in serum sodium concentration exceeds the limits we previously defined.

In established overly rapid correction, the benefits and harms of active treatments to re-lower serum sodium concentration have not been well studied. Nevertheless, the guideline development group feels that the dramatic consequences of osmotic demyelinating syndrome warrant an attempt to re-lower the serum sodium concentration in case of overly rapid correction using an active intervention.

It is plausible that overly rapid correction occurs more readily in conditions where treatment of the underlying cause results in restoration of the kidneys' capacity to excrete electrolyte-free water. Examples of such conditions include, but are not limited to, volume repletion in hypovolaemia, treatment of glucocorticoid deficiency, withholding thiazides,

withholding other drugs known to cause SIAD and lowering fluid intake in primary polydipsia. Based on these theoretical considerations, clinical experience and limited data, we believe that infusing electrolyte-free water (e.g. 5% glucose solutions) and/or injecting desmopressin can be used in experienced hands to re-lower serum sodium concentration in case of overly rapid correction.

However, the guideline development group was reluctant to advise it strongly without consulting an expert. Large multi-centre trials with these interventions are lacking. Overly rapid correction of hyponatraemia may indicate the presence of a complex case, where the effect of further treatment may be even more difficult to predict. We consider that seeking additional expertise may be the safest option in these conditions.

Suggestions for future research

- Additional prospective studies examining the combination of desmopressin and hypertonic saline to correct hyponatraemia and to avoid further overcorrection in those having already attained the correction limits are needed to further evaluate both the outcome benefits and harms of such a strategy.
- The combination of desmopressin and free water to reverse overcorrection needs further study.

Declaration of interest

We required all participants in the guideline development group to fill out a detailed 'Declaration of interest' including all the current and future conflicts of interest as well as past interest restricted to the 2 years before joining the guideline development process. Because it was judged that excluding every individual with some degree of potential conflict of interest would make assembling a guideline development group impossible, we allowed members of the guideline development group to have past financial and/or intellectual conflicts of interest. We did not attach any consequences to the stated interests, but rather insisted on transparency. All members of the guideline development group were allowed to participate in all the discussions and have equal weight in formulating the statements. All were allowed equal involvement in data extraction and writing the rationales. The declaration of interest forms are available from www.european-renal-best-practice.org/content/Joint-workgroup-hyponatraemia and are updated on a regular basis.

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society. Statutes and detailed standard operating procedures can be found on the ESICM website (www.esicm.org). ESICM receives funding through membership fees and revenues from its congresses, courses, educational ventures and journals. Activities of ERBP and its methods support team are supervised by an advisory board (see www.european-renal-best-practice.org for details and Declaration of interest). ERBP is an independent part of ERA–EDTA. The council of ERA–EDTA approves and provides the annual budget based on a proposition made by the chair of ERBP. ERA–EDTA receives money and is partly funded by industrial partners, but its council is not involved with and does not interfere with topic choice, question development or any other part of the guideline development process. Neither the societies nor the guideline development group received any funds directly from industry to produce this guideline.

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Appendix

Appendices are available online at <http://ndt.oxfordjournals.org>.

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Discussion

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General discussion

With this thesis, I aimed to contribute to evidence based practice in Nephrology. Not so much by expanding the theory of evidence based medicine, but by applying currently accepted methods to various aspects of evidence synthesis covering a wide array of clinical questions. Most of the work occurred as part of larger guideline development projects within European Renal Best Practice (ERBP), the official guideline development body of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA). In what follows, I will summarize the main results of each work, discuss their implication for practice and reflect on what I have learned from the experience.

Benefits and harms of interventions for children with primary vesicoureteric reflux

Primary VUR is thought to be a maturational defect, predisposing children for UTI, and renal involvement during UTI, and subsequently causing permanent kidney damage [1]. It is now recognised that at least some of the cortical defects detected after UTI are pre-existing developmental abnormalities rather than scars resulting from infection. What proportion of renal scarring is pre-existing and what proportion is secondary to infection remains unknown and controversial. The same applies in the considering long-term implications for future kidney function and hypertension [2, 3].

Treatment has traditionally been targeted at preventing recurrent UTI under the assumption this strategy would reduce the risk of symptomatic UTI and decrease involvement of the upper urinary tract; that it would mitigate kidney damage, and therefore reduce the risk of impaired renal function and hypertension in the future [4]. Long-term, low-dose antibiotics have predominantly been used when spontaneous resolution of VUR was to be expected, or surgical or endoscopic correction of VUR if those chances were considered slim [5].

We concluded that clinical decision making should balance the possible, but uncertain, reductions in repeat UTI and kidney scarring with a threefold increase in the risk of developing antibiotic resistance, a small risk of adverse antibiotic effects, the cost and inconvenience of daily antibiotic administration for often prolonged periods, and the potential to increase community antibiotic resistance to not only the organisms that cause UTI but also to other pathogenic organisms that would have otherwise responded to these medications. Our review provided no compelling evidence that low-dose long-term antibiotic prophylaxis reduced the risk of recurrent UTI in children with VUR. The synthesis favoured antibiotic treatment, but individual sample sizes were small, confidence intervals wide, and data quality variable. However, a concurrent systematic review including children both with and without VUR did find the reduction in repeat symptomatic UTI was statistically significant, indicating our findings may have resulted from limited power in the analysis. The estimate of absolute risk reduction for children with VUR equalled 8%, corresponding to a need to treat between 12 and 13 children for 12 months to prevent one symptomatic UTI. Antibiotic

prophylaxis seemed to reduce the risk of new or progressive kidney damage by 3%, corresponding to a number needed to treat of 33. The magnitude of these effects need to be considered in conjunction with the weight of the outcomes in decision-making. Given the fact that repeat UTI is usually not life-threatening and the consequence of a kidney scar for long-term kidney function is unclear, numbers needed to treat of 13 and 33 respectively may be considered quite high.

The incremental value of surgery over low-dose antibiotics largely remained uncertain. There was a small reduction in the risk of febrile UTI - with 8 children requiring surgery to prevent one episode of febrile UTI in 5 years - but not in symptomatic UTI overall. This modest benefit should be balanced against the possible risks of the surgical procedure. Correcting VUR using endoscopic approaches could theoretically reduce surgical risk, but to date, the few available randomized trial data do not suggest the reduction in febrile UTI risk confers a systematic reduction in kidney damage.

It is not unlikely that the grade of VUR modifies the effect various interventions have on the outcomes of interest. The studies assessing the effectiveness of antibiotic prophylaxis almost exclusively included children with lower grades of VUR (I to III), those evaluating the benefits and harms of surgical interventions exclusively included those with higher grades of VUR (IV to V). Although this represents the areas of perceived clinical uncertainty, it necessarily precludes any assessment of differential effect of treatments for children with high versus low grade VUR.

Sadly, our review did not identify any trials examining non-medical interventions, such as bladder and bowel management for dysfunctional elimination. In toilet-trained children with recurrent UTI, voiding postponement behaviours, incomplete emptying, and constipation are extremely common and may be much more important etiologic factors in UTI recurrence than the reflux itself [6, 7].

When we published our review in 2010, we suggested an additional well-designed, blinded and adequately powered study in children with VUR was needed to resolve the remaining uncertainty surrounding the benefit of antibiotic prophylaxis in preventing UTI and renal damage. In 2014, the results of such a study finally became available. The RIVUR study examined the effect of low-dose antibiotic treatment in children with various degrees of VUR on both symptomatic UTI and renal parenchymal injury assessed by DMSA scan [8]. The results confirmed our earlier findings of an 8% risk reduction in symptomatic UTI, but found the occurrence of renal scarring did not differ between the prophylaxis and placebo groups. To the inevitable question of whether I would advocate prophylactically treating children with long term-antibiotics after a first UTI, my answer, from a societal and professional perspective, would be no.

Pharmacokinetics, efficacy and safety of antidepressants for depression in stage 3–5 chronic kidney disease

At any given time and place, up to one quarter of the average dialysis unit will suffer

from major depression [9-11]. Even more will experience depressive symptoms. Aside from dramatically decreasing an often precarious quality of life to start with, it increases hospitalisation rates and shortens life expectancy [9, 12]. Accordingly, people with chronic kidney disease identify improving psychosocial aspects of living with their illness among their most important research priorities [13]. In response ERBP considered clinical depression and specifically the treatment of depression with antidepressants a priority topic for recommendation development.

Our systematic review found data were scarce and of generally poor quality. It showed that drug clearance in CKD3-5 was markedly reduced and dose-reduction necessary for several antidepressants: selegiline, amitriptyline, venlafaxine, desvenlafaxine, milnacipran, bupropion, reboxetine and tianeptine. In addition, it provided very limited evidence that treatment with antidepressants improved symptoms or overall quality of life. As such, we considered there was insufficient evidence for a general recommendation routinely advocating medical treatment in patients with CKD3-5 who suffer depression. However, there is substantial evidence available for the general population as well as for patient groups with chronic illnesses other than CKD, and the prevalence is high, the consequences for quality of life are dramatic; and the side effects of the studied antidepressants in CKD 3-5 fairly mild. Hence we judged an 8 to 12-week trial – with preferably a serotonin re-uptake inhibitor – could be considered in patients suffering from moderate depression according to DSM-IV. To avoid pointless prolonged treatment, the effect should be evaluated at the end of the trial period and treatment stopped if it appeared ineffective.

We highlighted the lack of high-quality efficacy and safety data on the use of antidepressants in advanced CKD and the need for a well-designed RCT to clarify the balance between benefits and harms. When our systematic review went to press, we knew of one ongoing randomized trial, comparing sertraline to placebo with a 12-week follow-up, aiming to include 200 patients (CAST-trial-NCT00946998). To this day, recruitment is still ongoing. It seems astounding that a problem so great both in numbers and clinical ramifications, continues to receive so little attention; how so few high-quality data on pharmacological treatment of depression in CKD are available. This situation forces us to rely on extrapolated evidence obtained from other patient groups, which may be inappropriate for all sorts of reasons. Yet, there are grounds for optimism. In the past six years, two influential journals in nephrology each published a randomized trial supporting non-pharmacological behavioural therapy for depression in CKD [14, 15]. Sample sizes were relatively small, and selection, performance and detection bias may have overestimated the effect sizes, but the focus on this topic shows an important shift of research towards patient-important issues.

European guideline on diagnosis and treatment of hyponatraemia: rationale and projects

Hyponatraemia is the most common electrolyte disorder in clinical medicine. Every fifth patient admitted to hospital through an emergency unit will have hyponatraemia. Hy-

ponatraemic patients have a 30% increased risk of death during hospitalisation and remain admitted 14% longer relative to those without hyponatraemia [16-18]. Determining management of hyponatraemia has always been problematic. Hyponatraemia develops under a variety of conditions and is accordingly dealt with by clinicians with diverse interests and expertise. Over the years, the treatment dilemma has fostered diverse speciality-based approaches to diagnosis and treatment and resulted in sometimes inconsistent guideline recommendations [19].

Clinicians who are frequently confronted with hyponatraemia, have often faulted existing guidance for being either too complex or too simplistic; for offering a diagnosis-, mechanism- or duration-based approach to treatment, failing to recognise that establishing the diagnosis, mechanism or duration of hyponatraemia may be difficult; for being biased by institution or speciality, limiting implementation across sites and clinical disciplines; for having a biochemical focus, failing to prioritise clinical status in decisions on treatment; or finally for not being evidence based.

Two evolving developments instigated European Renal Best Practice to re-examine the evidence for diagnosis and treatment of hyponatraemia: i) a clear recognition of the importance of evidence-based approaches to patient care to enhance quality, improve safety and establish a clear and transparent framework for service development and healthcare provision; ii) the advent of new diagnostics and therapeutics, highlighting the need for a valid, reliable and transparent process of evaluation to support key decisions [20].

To address this clinical dilemma we undertook two projects, which would feed the subsequent clinical practice guideline; a first intended to highlight both strengths and weaknesses of existing guidance, and a second aiming to identify benefits and harms of treatments for chronic non-hypotonic hyponatraemia.

Existing clinical practice guidelines and consensus statements on the diagnosis and treatment of hyponatraemia

Our review identified nine previously published guidance documents and showed that despite substantial similarities in proposed diagnostic tools, considerable differences indeed existed in classification thresholds, in when to initiate diagnostic work-up and in what sequence to order tests. Most existing guidance documents advocated similar first-line fluid treatments, but they differed somewhat in the limits for initial speed of increase in serum sodium concentration and which specific medications to use. Reasons for offering differing advice were undoubtedly multifactorial and at least partially related to limitations in the underlying evidence itself. Still, discrepancies between guidance documents could plausibly have originated from differences in underlying methods of development with overall quality being suboptimal at best.

This project was started as exploratory work prior to the development of the guideline, but finalised afterwards due to unforeseen delays in the peer review and editorial process for the projects' publication. Consequently, the systematic review ended up including also

the European guideline itself and measured its quality against that of those that had been published before. Overall, we scored very well in the domains scope and purpose and greatly exceeded the scores for other guidelines in rigour of development, an aspect of guideline development we had felt very strongly about [21]. We hope the obtained scores truly reflect stringent application of methodological standards that resulted in a 'trustworthy' clinical practice guideline. Yet, as four of the authors of the comparative paper were involved as well in developing the guideline and all others were people close to the guideline development group, one cannot rule out that a subconscious intellectual bias artificially inflated estimates of development rigour.

However, in the same analysis, the European guideline did not score equally well for other aspects related to guideline quality. We scored below 60%, which was poorer than a contemporary guideline, for applicability [22]. The score mostly reflected the absence of describing barriers to guideline implementation and failure to provide tools for putting the recommendations into practice. In part, guidelines are designed for practitioners to deal with the challenges of continuously growing medical knowledge and scientific information. They are designed to help make decisions at the moment care needs to be delivered. In its current format, mimicking a classic scientific paper, the European hyponatraemia document is admittedly too long, too unstructured and fails to present information in a layered fashion. It is not unlikely this will limit the extent to which the guideline will reach its target audience and stimulate implementation. On the other hand, the guideline did provide an algorithm for diagnosis and treatment. Although this should increase the utility of the guideline, it is unclear to what extent it will truly improve implementation of the recommendations.

Benefits and harms of interventions for chronic non-hypovolaemic hypotonic hyponatraemia

Until about a decade ago, hyponatraemia rarely found itself truly in the spotlight, whether within scientific journals or at professional society meetings. Treatments for chronic hyponatraemia had existed for years, but largely remained untested in the randomized trial setting. The regulatory approval of two vasopressin-receptor antagonists changed all that as industry launched a global campaign to sell to clinicians the importance of both chronic hyponatraemia as a problem and these new agents as its solution.

Our review identified 33 randomized trials, all save five investigating a vasopressin receptor antagonist. We found vasopressin receptor antagonists modestly raised serum sodium concentration (on average about 4 mmol/L) at the cost of a 10% increased risk of the rise being too rapid. To date little evidence from RCTs exists for a favourable effect on mortality, quality of life or any other truly patient-important health outcome. Studies contributing to the review included mostly participants with mild to moderate hyponatraemia (mean serum sodium concentration at study level ≥ 123 mmol/L). Meta-regression revealed a modifying effect of the serum sodium concentration at baseline, with lower values associ-

ated with larger increases and correspondingly more people with increases that were too rapid according to current standards. Extrapolation of meta-regression data would suggest higher increases, but possibly higher risks of rapid correction as the baseline serum sodium decreases. Although no study reported osmotic demyelination, it is unclear what would happen if vasopressin receptor antagonists were used on a larger scale and in people with sodium concentrations below those included in the RCTs that contributed to the review.

As hyponatraemia can develop in a variety of settings, it is not unreasonable to assume the effect of vasopressin-receptor antagonists may be different for different underlying conditions. There are two reasons for believing any differential effect of vasopressin receptor antagonists may be limited. First, meta-regression did not indicate that the cause of hyponatraemia modified the effect of vasopressin receptor antagonists on change from baseline in serum sodium concentration or any of the other outcomes. Second, the majority of studies that included participants with different underlying conditions, conducted some form of subgroup analysis. None showed appreciably different results according to the underlying condition.

Clinical practice guideline on the diagnosis and treatment of hyponatraemia

Aiming for harmonisation across disciplines, European Renal Best Practice decided to collaborate with the European Society of Intensive Care Medicine (ESICM) and the European Society of Endocrinology (ESE). It turned out to be a very fruitful partnership. Interactions between methodologists and clinicians in a truly multidisciplinary team safeguarded a commonality in view and resulted in a clinical practice guideline with the power to transcend the confines of individual subspecialty implementation.

The guideline suggested a diagnostic pathway that should allow reasonable discrimination between underlying causes so as to guide appropriate treatment. The main deviation from earlier algorithms was an initial reliance on urinary biochemical parameters and de-emphasis of volume-status. Contrary to common belief, even nephrologists seem poor at assessing fluid balance [23].

When it came to treatment, we attempted to resolve an ever resurfacing problem caused by treatment strategies essentially being dependent on the speed with which hyponatraemia develops. Focussing immediate decision-making on assessable symptoms rather than an estimate of time-frame removed at least some of the ambiguity earlier guidelines have been criticised for.

Extensive external review has suggested broad acceptance of the guideline content, with selected members of the ESICM, ESE and ERA-EDTA indicating recommendations were felt to be clear, acceptable and implementable [20]. Still, as it often is multifactorial, hyponatraemia remains a complex topic and no guideline can hope to fully disentangle the intricacies of differential diagnosis and treatment. Some of the champions of vasopressin receptor antagonists continue to have their reservations. They argue that if you accept important associations between hyponatraemia and adverse outcomes, and acknowledge

even mild hyponatraemia may cause, albeit mostly subtle symptoms, then how can a guidance group advise against the one treatment that has proven efficacy in raising serum sodium concentration? The answer lies in the a priori relative importance assigned to individual outcomes. For each intervention question, the guideline development group compiled a list of outcomes, reflecting both benefits and harms of alternative management strategies. They ranked the outcomes as critically, highly or moderately important according to their relative importance in the decision-making process. As such, patient-important health outcomes (reduction in all-cause mortality or improvement in quality of life, cognitive and general functional status) related to hyponatraemia and the treatment of hyponatraemia were considered critical. Owing to their surrogate nature, the outcomes 'change in serum sodium concentration' and 'correction of serum sodium concentration' were considered less important than the critically and highly important clinical outcomes. What is essential, is that all this happened *before* the data were collected and critically assessed. To date, clinically important outcomes remain insufficiently investigated in trials. The limited data we do have, suggest vasopressin receptor antagonists have little or no benefit on these outcomes for people with hyponatraemia. We do not debate whether vasopressin receptor antagonists are able to increase serum sodium concentration, because they do, at least in the short term. However, that by itself may not translate into an appreciable benefit, however much we would like it to. In the context of intervention studies, a surrogate is a measurable outcome such as a laboratory test, which responds to an intervention (e.g. lowering of cholesterol with statins) and is causally associated with a clinically important outcome (e.g. reduction in mortality with statins) [24]. Investigators often use surrogates instead of important health outcomes because surrogates can substantially reduce the cost, sample size and duration of a randomized trial. However, not all are valid proxies of clinically important outcomes. It is true that in acute and profound hyponatraemia, the evidence from observational studies is so overwhelming that we readily accept that increasing the serum sodium concentration is life-saving. It is also true that a chronically low serum sodium concentration is strongly and consistently associated with increased mortality and risk of bone fractures [18]. However, there is currently insufficient evidence that aside from affecting the surrogate (e.g. increase in serum sodium concentration with a vasopressin receptor antagonist) treatment in case of chronic hyponatraemia also changes the patient-centred outcomes downstream of the surrogate in the same causal pathway (e.g. reduction in mortality as a consequence of raising serum sodium concentration with a vasopressin receptor antagonist). In addition, the price paid for a 5 mmol/L increase in 290/1000 additional people, is an additional 29 having an increase exceeding 10-12 mmol/L/day, putting them at risk for osmotic demyelination syndrome. Although none of the participants in any of these randomised trials developed osmotic demyelination syndrome, in fact none were expected to. Although incidences are currently impossible to estimate, they are undoubtedly very low. Yet, it is precisely the fear of this rare but dramatic complication that has caused front-line clinicians to be extremely careful in the process of correcting hyponatremia. Throughout the guideline development process, the group tried to stick to the adagio 'Primum non nocere'.

General conclusion

Evidence-based practice of Nephrology is often challenged by a lack of high-quality evidence on the benefits and harms of tests and interventions. The studies conducted for this thesis predominantly highlight how limited the data for informed decision making sometimes are. It clearly limits the extent to which one can expect systematic reviews to provide insights beyond those provided by the individual studies and one may ask whether such studies are worth conducting at all. Of course, any attempt to answer the question somehow leads to a catch-22 situation, where utility can only be assessed ad-hoc and decisions have to be made regardless of whether or not high quality evidence exists.

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9

Personal reflections
and conclusions



Guideline development is hampered by the availability and quality of evidence

With this thesis I set out to contribute to evidence based practice by showing what worked and what didn't for various conditions in clinical nephrology. Instead, this exercise mostly revealed just how little we know of the diagnostics and therapeutics we use to prolong or improve the lives of the people we treat.

Unbiased and precise estimates of effect typically call for sizable randomised controlled trials. But such trials are costly and ill-afforded by most. As a consequence, the market is increasingly dominated by industry seeking to promote new – and often expensive – pharmaceuticals or devices. Interventions are compared with placebo – to obtain regulatory approval – or with control groups that are likely to produce 'sure wins' [1-3]; they measure surrogate rather than patient-important outcomes [4, 5]; and often stress the benefits and underplay the harms [6-10]. They often do not aim to entirely answer the questions that are relevant for clinical care. The way in which society values the achievements of independent researchers is partly responsible for this evolution. Novelty ignites excitement, begets scientific esteem, and is honoured both professionally and financially. Studies examining new tests and treatments are more thrilling to conduct, more likely to be read and thus more likely to be published than studies evaluating the benefits and harms of existing ones. As a consequence, existing – often less costly – alternatives often remain below the radar.

Where attempts are made to objectively examine what truly matters to patients, we are often limited by how researchers conduct and report their research. There is insufficient agreement on what outcomes matter, unsatisfactory guidance on how they should be measured and excessive variability in how they are reported. It makes effectively collating the research that is being done a tremendously challenging task with results that are often very difficult to interpret. Given the costs involved in conducting clinical studies, this lack of standardisation is a luxury we cannot afford.

Conclusions are highly dependent on what we do in the face of uncertainty

Clinical practice guidelines are often faulted for offering inconsistent recommendations and the suppliers of evidence remain a convenient culprit to blame. Still, methodological issues aside, it may not be so much a problem of the evidence we have, than what we do in the face of its absence. Consider a shortage of data on harms. If an intervention has a suggested benefit, do you believe withholding it does people disservice, or do you fear the unknown risk? This dilemma may explain some of the controversy we have seen around treatment of hyponatraemia with the 'vaptans' and the different viewpoint held by at least some of the American experts compared with the European guideline group. A witty collaborator nicely captured the sentiment by stating: 'It's what separates us from one another; in case of uncertainty, the Americans went west. We just stayed put.' In that sense, it may be more of a philosophical dispute than a methodological one, and possibly a much more difficult one to resolve.

Future perspectives

If we are adamant about resolving some of the raised concerns, we need to generate more evidence targeted at answering the questions that are truly relevant for clinical care. Guideline organisations need to work with systematic review groups and both should be involved in setting the research agenda while safeguarding it from industry lobby.

If we believe clinical practice recommendations have the ability to improve quality of care – it is an ethic premise for developing guidelines - then we need to spend more time and effort in bringing them to the bed-side. Research into the effectiveness of implementation strategies is paramount to ensuring restricted funds are allocated wisely.

Thus far, guideline development organisations have seldom integrated health-economic data into the equation. Yet, in an environment where resources are becoming exceedingly scarce, it is a responsibility physicians cannot continue to evade. Equally, guideline organisations need to address it too. Constructive integration of health-economics should aim to help understand key economic trade-offs between alternative management strategies, by summarising evidence for resource use, costs and cost-effectiveness from economic evaluations conducted in different settings and at different times, placed in the context of the best available evidence for management effects. It requires collaborative views on how health-economic data should be collated and incorporated into supranational decision-making. It requires guideline development groups to expand their methodological support to include people trained in health-economic synthesis. Be it difficult as it may, recommendations made without any reference to the implications for the sustainability of healthcare systems, are recommendations made into the void.

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Curriculum vitae

Personal information

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Nationality	Belgian
Date of birth	09-05-1981
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Education

2009-	Master in statistical data analysis – Faculty of Applied Mathematics, Ghent University, Belgium
2009-	PhD student in Medical Sciences, Faculty of Medicine, Ghent University, Belgium
2014	Legal degree of Specialist in Nephrology, Faculty of Medicine, Ghent University, Belgium
2013	Legal degree of Specialist in Internal Medicine, Faculty of Medicine, Ghent University, Belgium
2008	Postgraduate Degree in Acute Medicine -Theory. Belgian Society of Emergency and Disaster Medicine
2003	Postgraduate certificate in the basics of electrocardiography. Faculty of Medicine, Ghent University, Belgium
1999-2005	Master in medicine, Magna Cum Laude, Ghent Medical school, Ghent University, Belgium
1993-1999	Secondary education, Science-Mathematics, Koninklijk Atheneum Berchem, Belgium

Additional training courses

2011	Ghent-Oxford Summer School
2011	ASN Early program Glomerulonephritis
2010	Literature Searching Short Course, University of Sydney, Australia
2006	Advanced Life Support Provider Course. European Resuscitation Council

Clinical activities and positions

2014-	Resident Nephrology, Ghent University Hospital, Belgium
2013-2014	Assistant Specialist in Training Nephrology, Ghent University Hospital, Belgium
2009-2013	Assistant Specialist in Training Internal Medicine, Ghent University Hospital, Belgium
2008-2009	Assistant Specialist in Training Internal Medicine 3 rd year, Ghent University Hospital, Belgium
2007-2008	Assistant Specialist in Training Internal Medicine 2 nd year, OLV Aalst, Belgium
2006-2007	Assistant Specialist in Training Internal Medicine 1 st year, ASZ Aalst, Belgium

Academic activities and positions

2013-	Clinical Expert – European Medicines Agency
2012-2013	Honorary Research Fellow with Cochrane Renal Group and Center for Kidney Research, Westmead, NSW, Australia
2010	Honorary Research Fellow with Cochrane Renal Group and Center for Kidney Research, Westmead, NSW, Australia
2009-2013	Fellowship of the European Renal Best Practice, guideline writing body of ERA-EDTA

Editorial activities

2009-Present	Ad hoc reviewer for Acta Clinica Belgica
	American Journal of Kidney Diseases
	Annals of Internal Medicine
	British Medical Journal

Cochrane Database of Systematic Reviews
International Journal of Artificial Organs
Nephrology, Dialysis and Transplantation

Memberships of professional organisations

- 2012- European Renal Association –
European Dialysis Transplant Association (ERA-EDTA)
- 2011- Belgische Vereniging voor Nefrologie –
Société Belge de Nephrologie (BVN-SBN)

Foreign medical experience

- 2004 Clinical rotation Gynaecology, general surgery and dermatology at the
Azienda Ospedaliero Universitaria di Carregi, Florence, Italy

Scientific activities

Publications

1. **Nagler E**, Van Vlierberghe H, Colle I, Troisi R, de Hemptinne B. Impact of MELD on short-term and long-term outcome following liver transplantation: a European perspective. *Eur J Gastroenterol Hepatol* 2005;7(8):849-856.
2. **Nagler EV**, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD001532. DOI: 10.1002/14651858.CD001532.pub4.
3. Van Laecke S, **Nagler EV**, Vanholder R. Thrombotic microangiopathy: a role for magnesium? *Thrombosis Haemostasis* 2012;107(3):399-408.
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5. **Nagler EV**, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). *Nephrol Dial Transplant* 2012;27(10):3736-3745.
6. **Nagler EV**, Ball S. Quality assessment of clinical practice guidelines: who watches the watchmen? *Clin Endocrinol* 2013;78(2):181-182.
7. Vanmassenhove J, Vanholder R, **Nagler E**, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. *Nephrol Dial Transplant* 2013;28(2):254-73.

8. Van Laecke S, **Nagler EV**, Verbeke F, Van Biesen W, Vanholder R. Hypomagnesemia and the risk of death and GFR Decline in chronic kidney disease. *Am J Med* 2013;126(9):825-831.
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10. **Nagler EV**. Primary vesicoureteric reflux grade I to V: no compelling evidence for routine antibiotics or surgical intervention. *J Paediatr Child Health* 2013 Oct;49(10):876-879.
11. **Nagler EV**, Webster AC, Bolignano D, Haller MC, Nistor I, van der Veer SN, Fouque D, Van Biesen W. European Renal Best Practice (ERBP) Guideline development methodology: towards the best possible guidelines. *Nephrol Dial Transplant* 2014;29(4):731-738.
12. Bolignano D, **Nagler EV**, Van Biesen W, Zoccali C. Providing guidance in the dark: rare renal diseases and the challenge to improve the quality of evidence. *Nephrol Dial Transplant* 2013;29(9):1628-1632.
13. **Nagler EV**, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC. Interventions for chronic non-hypovolaemic hypotonic hyponatraemia. *Cochrane Database of Systematic Reviews* 2014. DOI: 10.1002/1465185.CD10965
14. **Nagler EV**, Vanmassenhove J, van der Veer SN, Nistor I, Van Biesen W, Webster AC, Vanholder R. Diagnosis and treatment of hyponatraemia: a systematic review of clinical practice guidelines. *BMC Medicine* 2014, 12:231-247.
15. Van Laecke S, **Nagler EV**, Taes Y, Van Biesen W, Peeters P, Vanholder R. The effect of magnesium supplements on early post-transplantation glucose metabolism: a randomized controlled trial. *Transpl Int* 2014; 27 (9): 895-902.
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18. Van Laecke S, **Nagler EV**, Vanholder R. The reply. *Am J Med* 2014;127(2):e15.
19. Haller C, van der Veer SN, **Nagler EV**, Tomson C, Lewington A, Hemmelgarn BR, Gallagher M, Rocco M, Obrador G, Vanholder R, Craig JC, Van Biesen W. A survey on the methodological processes and policies of renal guideline groups as a first step to harmonize renal guidelines. *Nephrol Dial Transplant* 2015;30(7):1066-1074.
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- tomatic bacteriuria in kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No.: CD011357. DOI: 10.1002/14651858.CD011357.
23. European Renal Best Practice. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant* 2015; 30(Suppl 2): ii1-ii142.
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25. Webster AC, **Nagler EV**, Gallagher M. Development of clinical practice guidelines in the care of people with kidney disease. *Am J Kidney Dis*. Accepted for publication.

Posters

1. **Nagler E**, Van Vlierberghe H, Troisi R, Colle I, De Vos M, de Hemptinne B. Higher MELD scores pre liver transplantation have no influence on the long term survival of the liver transplant patient. The International Liver Congress 2005 and 40th Annual Meeting of the European Association for the Study of the Liver, April 2004, Berlin, Germany.
2. **Nagler EVT**, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. 46th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology, 12-15 September 2010, Perth Convention Centre, Perth, Western Australia, Australia.
3. **Nagler EVT**, Webster AC, Vanholder R, Zoccali C. The pharmacokinetics of antidepressants for depression in stage 3 to 5 chronic kidney disease: a systematic review by European Renal Best Practice (ERBP). XLVIII ERA-EDTA Congress, June 2011, Prague, Czech Republic.
4. **Nagler EVT**, Webster AC, Vanholder R, Zoccali C. Efficacy and safety of antidepressants for depression in stage 3 to 5 chronic kidney disease: a systematic review by European Renal Best Practice (ERBP). Annual meeting of the Belgische Vereniging van Nephrologie – Société Belge de Nephrologie. Haut Ecole Libre de Bruxelles, Brussels, Belgium.
5. Van Laecke S, **Nagler EVT**, Verbeke F, Van Biesen W, Vanholder R. Serum magnesium as a predictor of decline of kidney function. ASN Kidney Week 8-13 November 2011, Philadelphia, USA.
6. Van Laecke S, **Nagler EV**, Van Biesen W, Jadoul M, Vanholder R. The association between serum magnesium and proton pump inhibitor use in chronic kidney disease. 49th ERA-EDTA Congress, May 2012, Paris, France.
7. Van Laecke S, Van Biesen W, **Nagler EV**, Taes Y, Peeters P, Vanholder R. The effect of mag-

- nesium supplementation on early post-transplantation glucose metabolism. 50th ERA-EDTA Congress, May 2013, Istanbul, Turkey.
8. Van Laecke S, Caluwe R, **Nagler EV**, Van Biesen W, Peeters P, Van Vlem B, Vanholder R. Insulin hyposecretion predicts non-response to magnesium supplementation in renal transplant recipients. 50th ERA-EDTA Congress, May 2013, Istanbul, Turkey.
 9. **Nagler EV**, Vanmassenhove J, van der Veer SN, Nistor I, Van Biesen W, Webster AC, Vanholder R. Diagnosis and treatment of hyponatraemia: a systematic review of clinical practice guidelines. 50th ERA-EDTA Congress, May 2013, Istanbul, Turkey.
 10. Haller MC, Van Biesen W, Webster AC, Vanholder R, **Nagler EV**. Correction speed limits for chronic hyponatraemia: a systematic review of observational data. 50th ERA-EDTA Congress, May 2013, Istanbul, Turkey.
 11. **Nagler EV**, Haller MC, Van Biesen W, Vanholder R, Webster AC. Treatments for chronic hyponatraemia: a systematic review of randomised controlled trials. 50th ERA-EDTA Congress, May 2013, Istanbul, Turkey.
 12. Van der Veer SN, Simon A, Weismann D, Lehner G, Coentrão L, Dongelmans D, Van Laecke S, Lapauw B, Ortiz A, Schiller A, Tesar V, **Nagler E**. Appraising implementability during the development process resulted in guideline revision. 10th G-I-N Conference, 18-21 August 2013, San Francisco, USA.
 13. Haller MC, **Nagler EV**, Van der Veer S, Nistor I, Bolignano D, Van Biesen W. A workflow checklist for improving management of the guideline development process. 10th G-I-N Conference, 18-21 August 2013, San Francisco, USA.
 14. **Nagler EV**, Liébaut V, Haller MC, Van der Veer S, Bolignano D, Nistor I, Van Biesen W. Developing a customised web-based data extraction tool using an existing customer relationship service: thinking outside the box. 10th G-I-N Conference, 18-21 August 2013, San Francisco, USA.
 15. Haller MC, Van der Veer SN, **Nagler EV**, Vanholder R, Craig JC, Van Biesen W. Towards harmonizing renal guidelines: an international survey of major guideline bodies. ASN Kidney Week 5-10 November 2013, Atlanta, USA.
 16. Nistor I, **Nagler EV**, Haller M, Bolignano D, Van Biesen W, van der Veer S. Identifying high priority topics for management of frail and elderly patients with chronic kidney disease (CKD) – scoping a European Guideline. 11th G-I-N Conference 20-23 August 2014, Melbourne, Australia.

National and international communications

1. Nagler EVT, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. 46th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology, 12-15 September 2010, Perth Convention Centre, Perth, Western Australia, Australia.
2. Nagler EVT, Webster AC, Vanholder R, Zoccali C. The efficacy and safety of antidepressants for depression in stage 3 to 5 chronic kidney disease: a systematic review by Eu-

- European Renal Best Practice (ERBP). XLVIII ERA-EDTA Congress, 23-26 June 2011, Prague, Czech Republic.
3. Nagler EVT, Webster AC, Vanholder R, Zoccali C. The pharmacokinetics, efficacy and safety of antidepressants for depression in stage 3 to 5 chronic kidney disease: a systematic review by European Renal Best Practice (ERBP). XLVIII ERA-EDTA Congress, 23-26 June 2011, Prague, Czech Republic.
4. Schwartz-Bartter Syndrome. SympoMed, Symposium spoedeisende geneeskunde, 9 September 2011. Haut Ecole Libre de Bruxelles, Brussels, Belgium.
5. Systematic literature searching, data extraction and evidence grading. First working meeting of EUDIAL – European Dialysis Working Group, a working group of ERA-EDTA, 13 October 2011, Paris, France.
6. Extracting evidence for a systematic review. 10th European Peritoneal Dialysis Meeting – EURO-PD, 21-24 October 2011.
7. Hyponatraemia guidelines in 2012: Evidence-based or industrial marketing strategy. Staff-meeting Internal Medicine, 10 May 2012, Ghent University Hospital, Ghent, Belgium.
8. Diagnosis and treatment of hyponatraemia in the ICU: The ERBP Guideline. 49th ERA-EDTA Congress, 24-27 May 2012, Paris, France.
9. New transplant guidelines. The 11th Renal Failure Academy, 4-7 July 2013, Mamaia, Romania.
10. How to retrieve the evidence from published research. The 11th European Peritoneal Dialysis Meeting, 11-14 October 2013, Maastricht, The Netherlands.
11. Disorders of the sodium balance. Vereniging van Geneesheren - Alumni Ghent University, 13 November 2013, Ghent, Belgium.
12. ERBP transplant guidelines and the challenge of uniting European Nephrologists. The annual congress of the Belgian Transplant Society, 27 March 2014, Brussels, Belgium.
13. Interpretatie van diagnostische testen. Evidence Based Medicine voor ManaMa, Ghent University, 22 March 2014, Ghent, Belgium.
14. Methods for searching the literature: why and how. ERA-EDTA how to retrieve evidence from the literature. 51st ERA-EDTA Congress, 31 May – 3 June 2014, Amsterdam, the Netherlands.
15. Can we assess individual risk for CKD and its progression based on risk scores? 51st ERA-EDTA Congress, 31 May – 3 June 2014, Amsterdam, the Netherlands.
16. Treatment of moderately and severely symptomatic hyponatraemia. 51st ERA-EDTA Congress, 31 May – 3 June 2014, Amsterdam, the Netherlands.
17. Transplant options in diabetics with advanced CKD. Swedish Internal Medicine Week - 2 October 2014, Göteborg, Sweden.
18. Diagnostic et prise en charge des hyponatrémies. 16^{ième} Réunion Commune Société de Néphrologie, Société Francophone de Dialyse - 3 October 2014, St Etienne, France.
19. l'Analyse critique d'un essai thérapeutique. 13^{ième} Congrès national de Néphrologie, 19 février 2015, Marrakech, Morocco.

20. Approche étiologique et prise en charge d'une hyponatrémie. 13^{ième} Congrès national de Néphrologie, 21 février 2015, Marrakech, Marocco.
21. European guideline on diagnosis and treatment of hyponatraemia. 21^{ste} Edition dialysis symposium Jemeppe, Hargimont, Belgium.
22. Asking the right questions: an example of the elderly guideline. 52nd ERA-EDTA Congress, 28-31 May 2015, London, UK.

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My dear friends. You have seen the best and worst of me. Some of you went, but remarkably, many of you stayed. Thank you for reminding me that there is more to life than achievement alone and that it only counts if the road is worth the journey.

My brothers. If I am at all verbally agile, I have you to thank for it. It developed as a mechanism for survival during my formative years. And Wimpie, there is no shame in not having a PhD, we love you regardless.

My wonderful father. At 34 I am still your little girl. I suspect it is what I will stay for the remainder of both our lives. Work in health-care and current day reality has made me see just how privileged that life has been so far. You've brought me up in a world that's safe and carefree, knowing I have you to pick me up should ever I fall.

And finally, my darling mom. To whom this thesis is dedicated. Whose unacknowledged one-liners include: 'Quitting is not in the dictionary, and neither is I can't'. If I live my life according to my own premises, it is because you taught me to. If I grew up believing I could achieve anything I wanted to, it is because you led by example. And so, should you ever again doubt it in the future, read this and rest assured: I could not have wished for a better mother.

- Evi -